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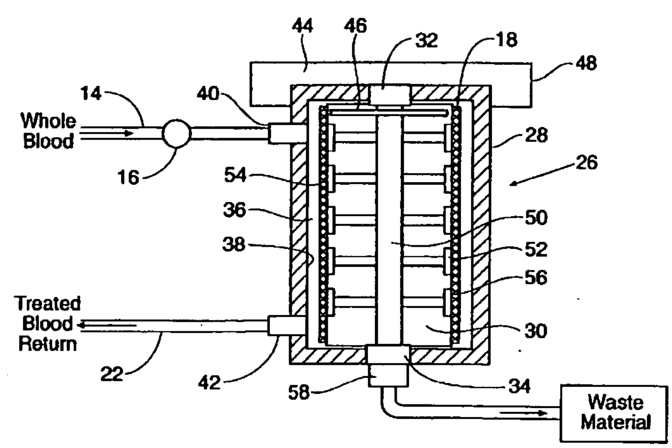
(54) Title: SHEAR-ENHANCED SYSTEM AND METHODS FOR REMOVING WASTE MATERIALS AND LIQUID FROM THE BLOOD



(57) Abstract: Systems and methods convey the blood through a gap (36) defined between an inner surface (30) that is located about an axis and an outer surface (38) that is concentric with the inner surface (30). At least one of the inner and outer surfaces (30,38) carries a membrane (18) that consists essentially of either a hemofiltration membrane or a hemodialysis membrane. The systems and methods cause relative movement between the inner and outer surfaces (30,38) about the axis at a selected surface velocity, taking into account the size of the gap (36). The relative movement of the two surfaces (30,38) creates movement of the blood within the gap (36), which creates vortical flow conditions that induce transport of cellular blood components from the membrane (18) while plasma water and waste material are transported to the membrane (18) for transport across the membrane (18).

WO 03/066200 A1

SHEAR-ENHANCED SYSTEMS AND METHODS FOR REMOVING WASTE MATERIALS AND LIQUID FROM THE BLOOD

Field of the Invention

This invention relates to systems and methods that remove waste materials and liquid from the blood of an individual whose renal function is impaired or lacking.

Background of the Invention

For various reasons, including illness, injury or surgery, patients may require replacement or supplementation of their natural renal function in order to remove excess fluid or fluids containing dissolved waste products from their blood. Several procedures known for this purpose are hemodialysis, hemofiltration, hemodiafiltration and ultrafiltration.

Summary of the Invention

The invention provides shear-enhanced systems and methods for removing waste materials and liquid from the blood.

The systems and methods convey the blood through a gap defined between an inner surface that is located about an axis and an outer surface that is concentric with the inner surface. At least one of the inner and outer surfaces carries a membrane that consists essentially of either a hemofiltration membrane or a hemodialysis membrane. The systems and methods cause relative movement between the inner and outer surfaces about the axis at a selected surface velocity, taking into account the size of the gap. The relative movement between the inner and outer surfaces creates movement of

the blood within the gap, which creates a vortical flow condition that induces transport of cellular blood components from the membrane while plasma water and waste material are transported to the membrane for transport across the membrane.

The circulatory forces of the vortical flow condition clear the membrane surface of occluding cellular components to maintain efficient operation. The circulatory forces also supplement the shear forces exerted on the blood by viscous drag. Due to the circulatory forces, the concentration of waste materials in the blood plasma water becomes more homogenous. As a result, the transport of waste materials and associated blood plasma water across the membrane is significantly enhanced. Shear-enhanced waste removal makes possible the use of smaller processing devices and/or processing at reduced blood flow rates.

Brief Description of the Drawings

Fig. 1 is a schematic view of a system that includes a blood processing unit for removing waste material and plasma water from the blood;

Fig. 2 is a side section view of one embodiment of a blood processing unit that the system shown in Fig. 1 can incorporate for the purpose of performing shear-enhanced hemofiltration;

Fig. 3 is a side section view of another embodiment of a blood processing unit that the system shown in Fig. 1 can incorporate for the purpose of performing shear-enhanced hemodialysis;

Fig. 4 is a side section view of another embodiment of a blood processing unit that the system shown in Fig. 1 can incorporate for the purpose of performing shear-enhanced hemodialysis;

Fig. 5 is a side section view of another embodiment of a blood processing unit that the system

shown in Fig. 1 can incorporate for the purpose of performing shear-enhanced hemofiltration and hemodialysis;

Fig. 6 is an enlarged and simplified perspective view of a gap formed between a stationary and rotating concentric surfaces, of a type that the blood processing units shown in Figs. 2 to 5 incorporate, in which vortical flow conditions provide shear-enhanced waste material and plasma water removal; and

Fig. 7 is an enlarged side sectional view of the vortical flow conditions shown in Fig. 5 that provide shear-enhanced waste material and plasma water removal.

The invention may be embodied in several forms without departing from its spirit or essential characteristics. The scope of the invention is defined in the appended claims, rather than in the specific description preceding them. All embodiments that fall within the meaning and range of equivalency of the claims are therefore intended to be embraced by the claims.

Description of the Preferred Embodiments

Fig. 1 shows a system 10 for removing waste material (e.g., urea, creatinine, and uric acid) and plasma water from the blood of an individual whose renal function is impaired or lacking. The system 10 includes a blood processing unit 12 that receives whole blood from the individual. The individual typically has one or more surgically installed vascular access devices, such as an arterial-venous fistula, to facilitate coupling the blood processing unit 12 to the circulatory system of the individual. In the illustrated embodiment, arterial whole blood is drawn from the individual through an inlet path 14. An inlet pump 16 governs the blood inlet flow rate.

The blood processing unit 12 includes a membrane 18, along which the whole blood drawn from the individual is conveyed. The membrane 18 can have

different functional and structural characteristics, which affect the manner in which waste material is transported by the membrane 18. Generally speaking, waste material carried in blood plasma water can be separated by the membrane 18 from the whole blood either by convective transport, which is driven by pressure differentials across the membrane (in a process known as hemofiltration), or by diffusion, which is driven by concentration gradients across the membrane (in a process known as hemodialysis). The waste materials and associated blood plasma water are removal from the blood processing unit 12 through a waste path 20 for discard.

The pores of the membrane 18 desirably have a molecular weight cut-off that block the passage of cellular blood components and larger peptides and proteins (including albumin) across the membrane. These components are retained in the blood, which is conveyed from the blood processing unit 12 through an outlet path 22 for return to the individual. In the illustrated embodiment, the treated blood is returned to the venous blood circulatory system of the individual.

Fresh physiologic fluid, called replacement fluid, is typically supplied from a source 24 to the plasma water and toxin-depleted blood. The replacement fluid restores, at least partially, a normal physiologic fluid and electrolytic balance to the blood returned to the individual.

The relative volumes of waste plasma water removed and replacement fluid supplied can be monitored, e.g., by gravimetric means, so that a desired volumetric balance can be achieved. An ultrafiltration function can also be performed by the blood processing unit 12, by which plasma water is replaced in an amount slightly less than that removed. Ultrafiltration decreases the overall fluid level of the individual undergoing treatment, which

typically increases due to normal fluid intake between treatment sessions.

The blood processing unit 12 includes a processing cartridge 26, in which the membrane 18 is housed. The cartridge 26 is desirable disposable and, in one representative embodiment (see Fig. 2), includes a generally cylindrical housing 28, which is sized to be conveniently manipulated by an operator. The housing 28 can be oriented for use either horizontally or vertically, or any intermediate position.

An elongated cylindrical rotor 30 (which can also be called a "spinner") is rotatably supported within the housing 28 between oppositely spaced pivot bearings 32 and 34. The rotor 30 rotates within the housing 28, which is held stationary during use. However, other manners of operation are possible, and the housing need not be held stationary.

An annular gap 36 is formed between the outer surface of the rotor 30 and the interior wall 38 of the housing 28. Whole blood in the inlet path 14 is conveyed through a blood inlet port 40 into the gap 36 for processing by the inlet pump 16. After processing, the blood is discharged from the gap 36 through an oppositely spaced outlet port 42, whioh communicates with the blood return path 22.

In the illustrated embodiment, a magnetic drive assembly 44 provides rotation to the rotor 30. A ring of magnetic material 46 in the rotor 30 is acted upon by a rotating magnetic field generated by an external, rotating magnetic drive member 48, which releasably engages the adjacent end of the housing 28 for use. The rotor 30 rotates relative to the stationary interior wall 38 of the housing 28. The magnetic drive member 48 rotates,the rotor 30 at a predetermined angular velocity.

Further details regarding devices employing a

spinning rotor and a stationary housing for blood filtration can be found in United States Patent No. 5,194,145 and United States Patent No. 4,965,846, which are incorporated herein by reference.

Further details of construction and operation of the processing cartridge 26 can differ, depending upon the type of blood processing sought to be performed. If hemofiltration is to be performed, the membrane 18 comprises an appropriate hemofiltration membrane (as Fig. 2 shows). If hemodialysis is to be performed, the membrane 18 comprises an appropriate hemodialysis membrane (as Figs. 3 and 4 show). If hemodialysis with hemofiltration is to be performed, the processing cartridge 26 can include both a hemofiltration membrane and a hemodialysis membrane (as Fig. 5 shows).

A. Hemofiltration

In the embodiment shown in Fig. 2, the rotor 30 has an internal cavity 50 bounded by a grooved cylindrical wall 52 forming a network of channels 56. A hemofiltration membrane 54 covers the outer surface of grooved wall 52. The hemofiltration membrane 54 can comprise, e.g., a biocompatible synthetic material such as polysulfone, polyacrylonitrile, polymethylmethacrylate, polyvinyl-alcohol, polyamide, polycarbonate, etc., and cellulose derivatives. The pores of hemofiltration membrane 54 desirably allow passage of molecules up to about 30,000 Daltons, and desirably not greater than about 50,000 Daltons, to avoid the passage of albumin (molecular weight of 68,000 Daltons).

The network of channels 56 convey blood plasma water passing through the membrane 54 into the cavity 50. An outlet port 58 communicates with the cavity 50 to convey blood plasma water from the processing cartridge 26.

In operation, as the rotor 30 is rotated, the pump

16 conveys whole blood into the gap 36. The whole blood flows within the gap 36 in contact with the hemofiltration membrane 54.

In response to the transmembrane pressure created by the pump 16, waste material and associated blood plasma water flow from the gap 36 through membrane 54 into the channels 56. Waste material and associated blood plasma water are discharged from the processing cartridge through the outlet port 58. Cellular blood components continue to flow within the gap 36 for discharge through the outlet port 42.

It should be appreciated that, alternatively, the hemofiltration membrane 54 can be mounted on the stationary wall 38 of the housing 28, instead of being mounted on the spinning rotor 30, as Fig. 2 shows. In this arrangement, the network of channels 56 communicating with the waste outlet port 58 would be formed in the stationary wall 38, and the membrane 54 would overlay the channels in the same fashion shown in Fig. 2. It should also be appreciated that, alternatively, a hemofiltration membrane 54 can be mounted on both the spinning rotor 30 and the stationary wall 28 and used in tandem for waste material and plasma water removal.

B. **Hemodialysis**

In the embodiment shown in Fig. 3, the interior wall 38 of the housing 28 has a network of channels 60 communicating with an inlet port 62 and an outlet port 64. A semipermeable hemodialysis membrane 66 overlays the network of channels 60. The membrane 66 can, e.g., comprise a medium to high flux membrane, for example, a polysulfone, cellulose triacetate or acrylonitrile membrane. Such membranes are typically well suited to fluid and small solute (less the 10,000 Daltons) removal. One side of the membrane 66 faces the annular gap 36 and

the rotor 30, which, in the illustrated embodiment, carries no membrane. The other side of the membrane 66 faces the channels 60.

In operation, as the rotor 30 is rotated, the pump 16 conveys whole blood into the gap 36. The whole blood flows within the gap 36 in contact with membrane 66. Fresh dialysate is circulated by a pump 70 from a source 68 through the channels 60 via the ports 62 and 64. Desirably (as Fig. 3 shows), the dialysate is circulated through the channels 60 in a flow direction opposite to the direction of whole blood flow in the gap 36.

As blood flows through the gap 36, plasma water is conveyed across the membrane 66 due to transmembrane pressure created by the pump 16. Targeted waste materials are also transferred across the membrane 66 by diffusion, due to a difference in concentration of these materials in the blood (high concentrations) and in the fresh dialysate (low concentrations). In response to the high-to-low concentration gradient, waste materials flow from the gap 36 through the membrane 66 into the dialysate. The waste materials are discharged with the spent dialysate out of the processing cartridge 26 to, e.g., a drain. Cellular blood components continue to flow within the gap 36 for discharge through the outlet port 42 for return to the individual.

As shown in Fig. 4, in an alternative embodiment, the rotor 30 can include a network of channels 72 through which dialysate can be circulated in the manner just described. In this arrangement, a hemodialysis membrane 74 overlays the network of channels 72 on the rotor 30. One side of the membrane 74 faces the annular gap 36. The other side of the membrane faces the channels 72.

It should be appreciated that the hemodialysis membrane 74 on the rotating rotor 36 can also be used in combination with the hemodialysis membrane 66 on the

stationary interior wall 38 of the housing 28, or by itself (in which case the stationary interior wall 38 of the housing 28 would be free of a membrane.

As shown in Fig. 5, the processing cartridge 26 can include a hemodialysis membrane 66 mounted on either the rotor 30 or the interior housing wall 38 and a hemofiltration membrane 54 mounted on the other location. In this arrangement, the processing cartridge 26 accommodates hemdialysis with hemofiltration, a process also called hemodiafiltration.

C. **Shear-Enhanced Waste Removal**

In an annular gap 36 as just described, which is defined between two concentric surfaces (e.g., the rotor 30 and the interior housing wall 38), rotation of the inner surface relative to the outer surface can induce vortical flow conditions in the blood residing in the gap 36. The vortical flow conditions take the form of successive, alternately circulating, annuli TV (see Fig. 6) in the gap 36 between the two concentric surfaces. This vortex action can be a type that can be generally classified as "Taylor vortices" (as designated as TV in Fig. 6). The nature of the Taylor vortices can vary among laminar stable Taylor vortices, wavy non-stable Taylor vortices, turbulent Taylor vortices, or other intermediate vortical flow conditions.

Taylor vortices will develop in the blood occupying the gap 36, regardless of whether the membrane is mounted on the inner surface or on the outer surface, or both surfaces. Taylor vortices develop in the blood occupying the gap 36 as a result of relative movement between the inner and outer surfaces, regardless of whether one of the surfaces is held stationary while the other rotates, or whether both surfaces are allowed to rotate. To achieve desired vortical flow conditions, it is believed that the inner surface should be rotated relative to the the

outer surface, and, if the outer surface is allowed to rotate, the rate of rotation of the inner surface should exceed the rate of rotation of the outer surface.

The amplitude of the vortex action, which is characterized by the Taylor number, is a function of the rate of rotation of the rotating surface and the radial dimension of the gap 36. At a given radial dimension, increasing the rate of rotation will increase the amplitude of the vortex action, leading to a higher Taylor number. Given a rate of rotation, narrowing the radial dimension of the gap 36 will also increase the amplitude vortex action, leading to a higher Taylor number. It is believed that radial dimension of the gap 36 and the rate of rotation should be selected to yield a Taylor number that is greater than the critical Taylor number, at which vortical flow conditions develop.

Transmembrane pressure is also desirably monitored and maintained (by controlling operation of the pump 16) at a magnitude that maximizes fluid transport across the membrane without driving cellular blood components into the membrane pores, which can cause membrane plugging, hemolysis, and trauma to fragile cellular blood components residing within the gap 36.

When maintained within desired limits, the vortical flow conditions provide a sweeping action in the gap 36 (see Fig. 7) that transports cellular blood components away from the membrane while blood plasma water carrying the targeted uremic toxins is transported to the membrane for passage through the pores of the operative membrane. The circulation caused by the vortical flow conditions removes adherent cellular blood components from the surface of the operative membrane and replenishes available blood plasma water for transport through the membrane pores. The vortical flow conditions thereby clear the membrane surface of occluding cellular

components to maintain efficient operation at desirable transmembrane pressure levels. The circulatory forces also supplement the shear forces exerted on the blood by viscous drag, which is tangential to the spinning membrane surface. Furthermore, due to the circulatory forces, the concentration of waste materials in the blood plasma water becomes more homogenous. In all, the transport of waste materials and associated blood plasma water across the membrane is significantly enhanced. Shear-enhanced waste removal makes possible the use of smaller processing devices and/or processing at reduced blood flow rates.

If desired, ultrafiltration volume can be augmented by placing, either upstream or downstream of the processing cartridge 26, an auxiliary processing cartridge 76 (shown in phantom lines in Fig. 1). The auxiliary processing cartridge 76 subjects the blood to plasma water removal (either by hemodialysis or hemofiltration) in addition to the plasma water removal by the processing cartridge 26. An auxiliary processing cartridge 76 can also be used in series with the processing cartridge 26, to provide waste removal by hemofiltration to augment waste removal by hemodialysis conducted by the processing cartridge 26, or vice versa.

Various features of the invention are set forth in the following claims.

We Claim:

1. A system for removing waste from the blood of an individual comprising

a blood processing device comprising a gap defined between an inner surface that is located about an axis and an outer surface that is concentric with the inner surface, at least one of the inner and outer surfaces carrying a membrane that consists essentially of at least one of a hemofiltration membrane and a hemodialysis membrane, and

a drive mechanism causing relative movement between the inner and outer surfaces about the axis at a selected surface velocity, taking into account the size of the gap, to create movement of the blood within the gap that induces transport of cellular blood components from the membrane while plasma water and waste material are transported to the membrane for transport across the membrane.

2. A system according to claim 1

wherein the membrane comprises a hemofiltration membrane.

3. A system according to claim 2

wherein the hemofiltration membrane includes a first surface facing toward the gap and a second surface facing away from the gap, and

wherein the blood processing device includes a channel along the second surface of the hemodialysis membrane to convey waste material transported across the hemofiltration membrane.

4. A system according to claim 1

wherein the membrane comprises a hemodialysis membrane.

5. A system according to claim 4

wherein the hemodialysis membrane includes a first surface facing toward the gap and a second surface

facing away from the gap, and

wherein the blood processing device includes a channel to convey a dialysate along the second surface of the hemodialysis membrane to create a concentration gradient across the hemodialysis membrane to transport waste material from the blood, and

further including a source of dialysate communicating with the channel.

6. A system according to claim 1

wherein the drive mechanism rotates the inner surface while holding the outer surface stationary.

7. A system according to claim 1

wherein the drive mechanism rotates the inner surface at a higher rate of rotation than the outer surface.

8. A system according to claim 1

wherein both surfaces carry a membrane that consists essentially of at least one of a hemofiltration membrane and a hemodialysis membrane.

9. A system according to claim 8

wherein both surfaces carry a hemodialysis membrane.

10. A system according to claim 8

wherein both surfaces carry a hemofiltration membrane.

11. A system according to claim 8

wherein one of the surfaces carries a hemofiltration membrane and the other surface carries a hemodialysis membrane.

12. A method for removing waste from the blood of an individual comprising the steps of

conveying the blood through a gap defined between an inner surface that is located about an axis and an outer surface that is concentric with the inner surface, at least one of the inner and outer surfaces

carrying a membrane that consists essentially of at least one of a hemofiltration membrane and a hemodialysis membrane, and

causing relative movement between the inner and outer surfaces about the axis at a selected surface velocity, taking into account the size of the gap, to create movement of the blood within the gap that induces transport of cellular blood components from the membrane while plasma water and waste material are transported to the membrane for transport across the membrane.

13. A method according to claim 12

wherein the membrane comprises a hemofiltration membrane.

14. A method according to claim 13

further including the step of conveying away waste material that is transported across the hemofiltration membrane.

15. A method according to claim 12

wherein the membrane comprises a hemodialysis membrane.

16. A method according to claim 15

further including the step of conveying a dialysate along an opposite side of the hemodialysis membrane to create a concentration gradient across the hemodialysis membrane to transport waste material from the blood.

17. A method according to claim 12

wherein the inner surface is rotated while holding the outer surface stationary.

18. A method according to claim 12

wherein the inner surface is rotated at a higher rate of rotation than the outer surface.

19. A method according to claim 12

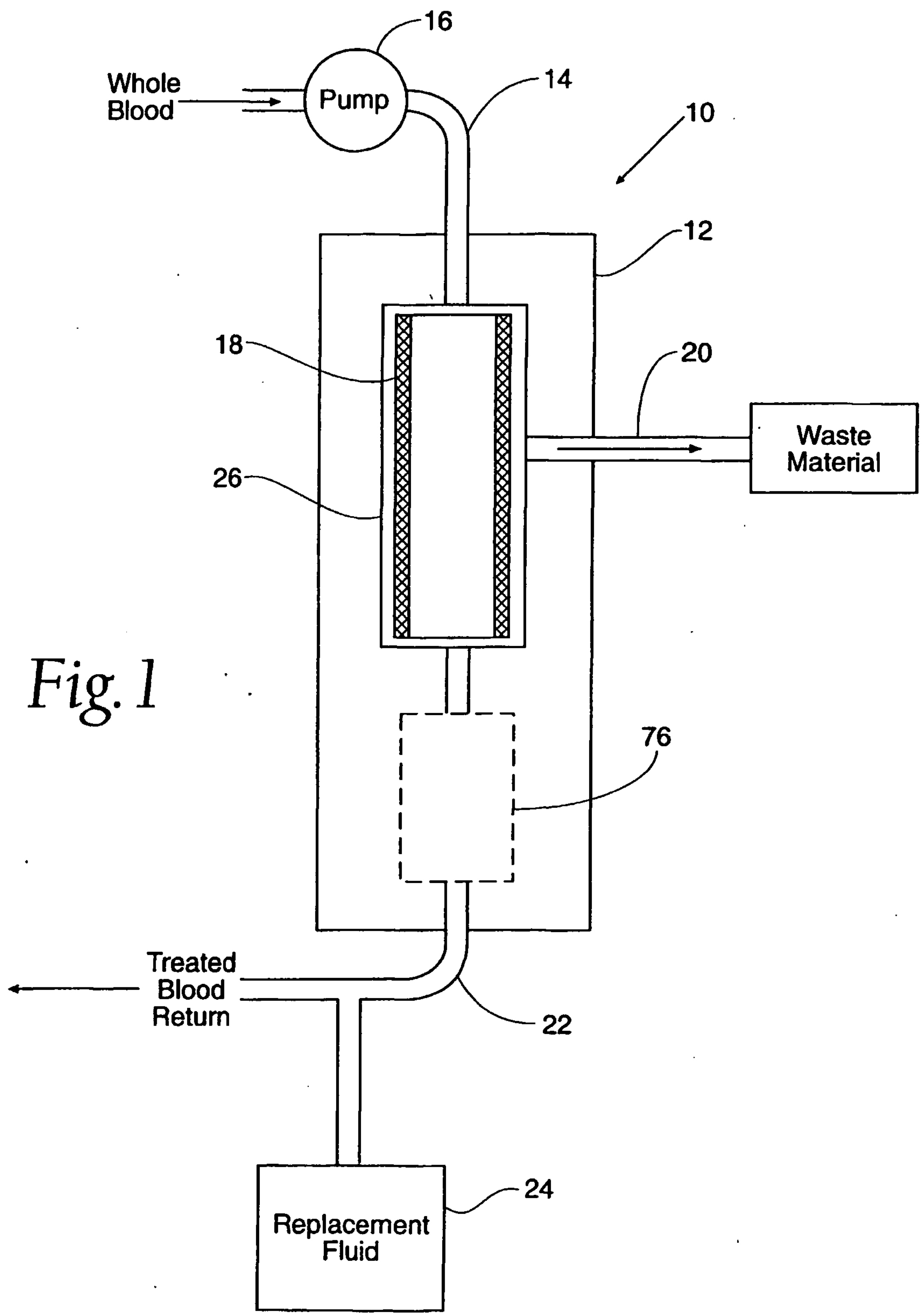
wherein both surfaces carry a membrane that consists essentially of at least one of a hemofiltration

membrane or a hemodialysis membrane.

20. A method according to claim 19 wherein both surfaces carry a hemodialysis membrane.

21. A method according to claim 19 wherein both surfaces carry a hemofiltration membrane.

22. A method according to claim 19 wherein one of the surfaces carries a hemofiltration membrane and the other surface carries a hemodialysis membrane.


16
Whole
Blood
Pump
14
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12
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Waste
Material
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76
Treated
Blood
Return
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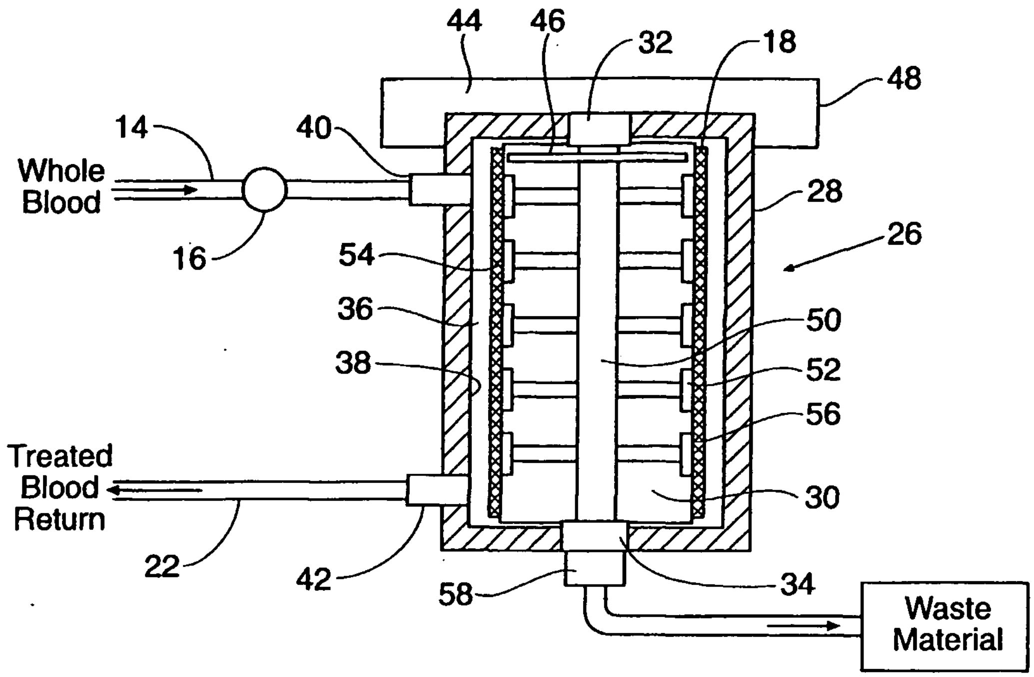
24
Replacement
Fluid

Fig. 1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58
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Waste Material

Fig. 2

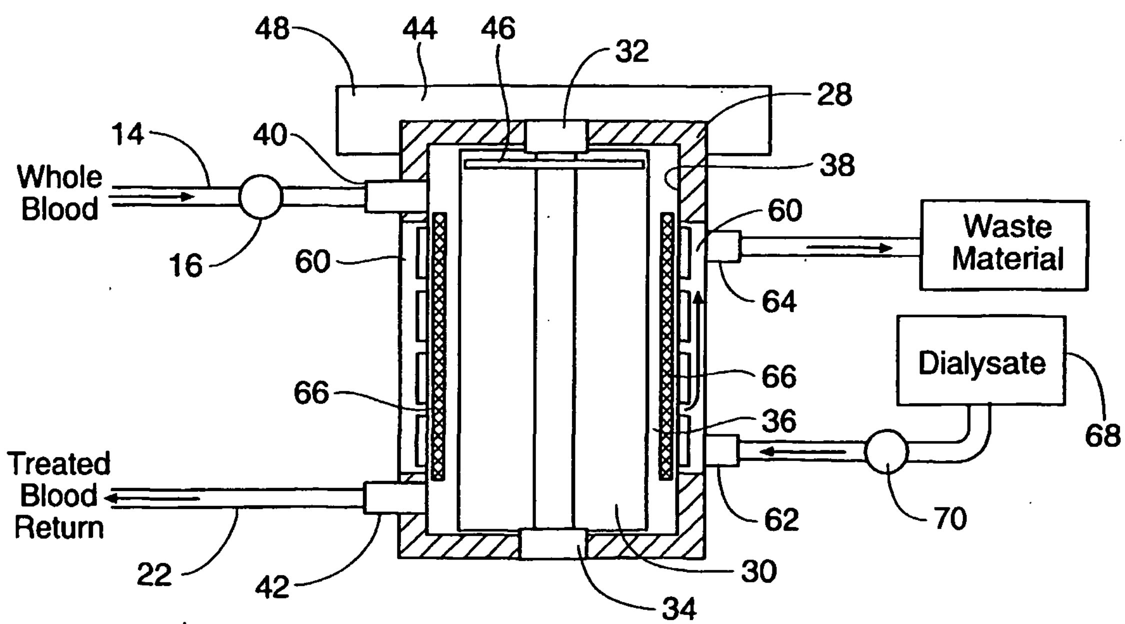
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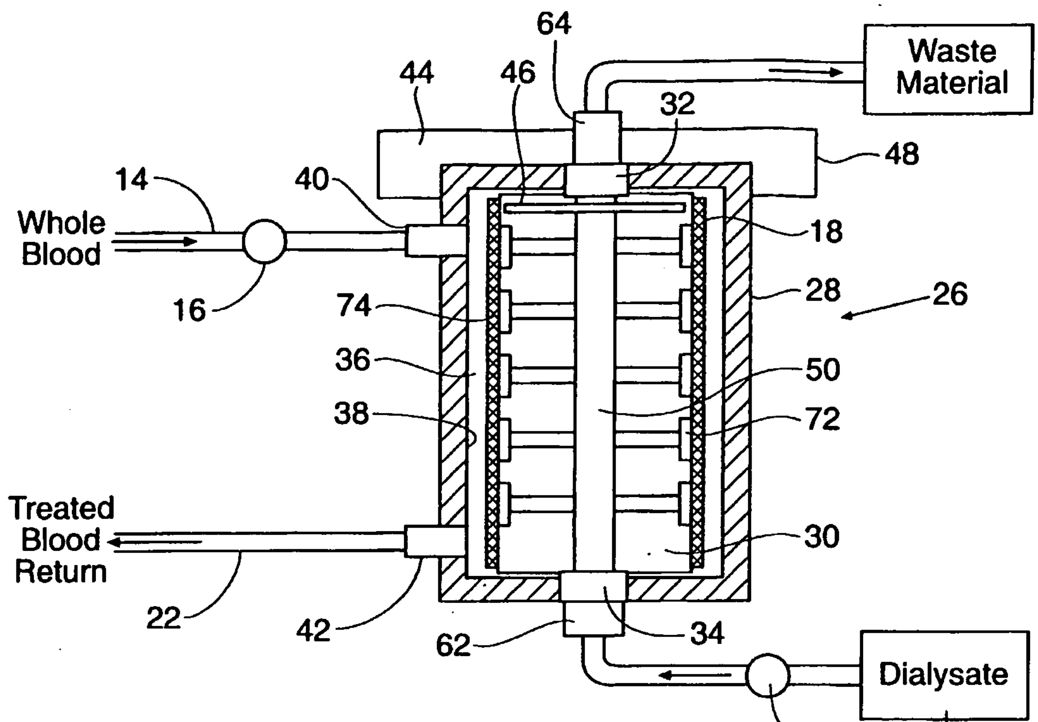
Fig. 3



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Treated Blood Return
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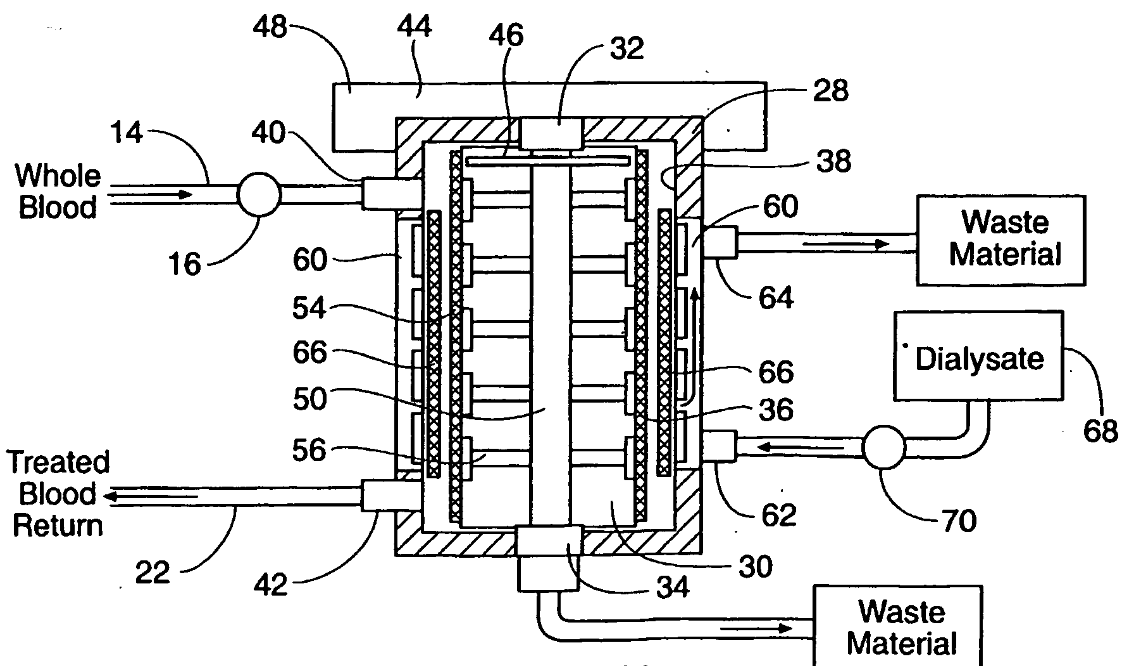
Fig. 4



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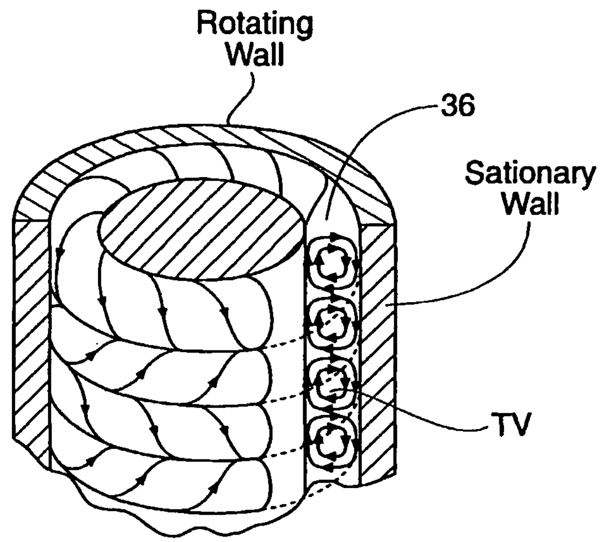
Waste Material

Fig. 5


Rotating
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Wall
TV

Fig. 6

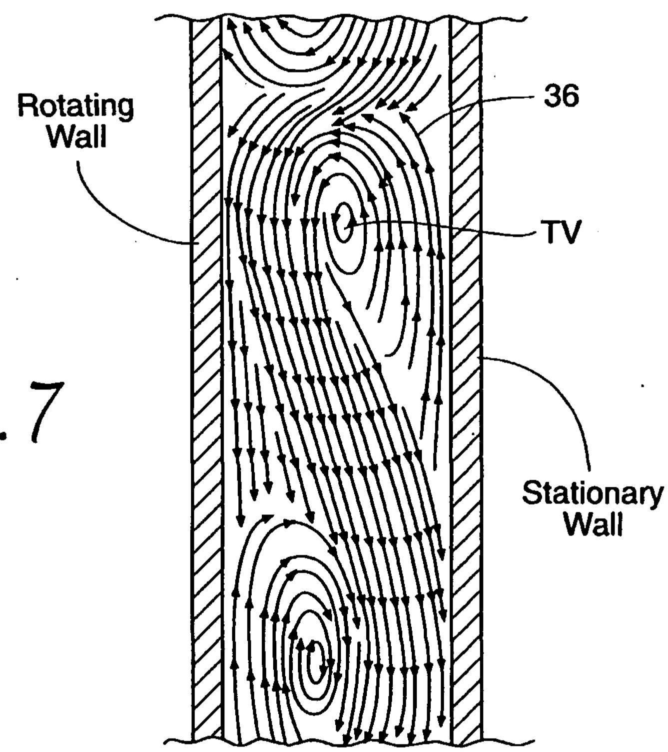
Rotating
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Fig. 7

INTERNATIONAL SEARCH REPORT

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PCT/US03/02442

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : B01D 61/00, 61/14, 61/18, 61/24, 61/28, 63/16
US CL : 210/321.67, 321.68, 321.78, 360.1, 645, 646, 650
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 210/321.67, 321.68, 321.78, 360.1, 645, 646, 650

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,194,145 A (SCHOENDORFER) 16 March 1993 (16.03.1993), see entire document.	1-3, 6-7, 12-14, 17-18
X	US 6,099,730 A (AMEER et al) 08 August 2000 (08.08.2000), see entire document.	1-2, 6-8, 10, 12-14, 17-19, 21
Y	US 4,790,942 A (SHMIDT et al) 13 December 1988 (13.12.1988), see entire document.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search 17 April 2003 (17.04.2003)	Date of mailing of the international search report 01 MAY 2003
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(54) Title: VORTEX ENHANCED FILTRATION DEVICE AND METHODS

(57) Abstract: Preferred aspects of the present invention relate to advances in rotating, vortex-enhanced reverse osmosis filtration. More particularly, the filtration device and methods incorporate a rotational drive mechanism adapted to use the flow of pressurized process fluid to cause rotation of a rotor within a housing, thereby creating shear and Taylor vortices in the gap between the rotor and housing. The improvements disclosed herein facilitate continuous use of vortex-enhanced filtration for prolonged periods of time.

VORTEX ENHANCED FILTRATION DEVICE AND METHODS

Background of the Invention

Field of the Invention

Preferred aspects of the present invention relate to rotating reverse osmosis (RO) filtration, wherein filtrate flux is enhanced by creation of shear and Taylor vortices in the coaxial gap between a RO membrane and a cylindrical wall of the filtration device.

Description of the Related Art

One of the most limiting problems in filtration is filter clogging, scientifically described as "concentration polarization." As a result of the selective permeability properties of the filter, the filtered material that cannot pass through the filter becomes concentrated on the surface of the filter. This phenomenon is clearly illustrated in the case of a "dead-end" filter, such as a coffee filter. During the course of the filtration process, the filtered material (coffee grounds) building up on the filter creates flow resistance to the filtrate, the fluid (coffee) which can pass through the filter. Consequently, filtrate flux is reduced and filtration performance diminishes.

Various solutions to the problem of concentration polarization have been suggested. These include: increasing the fluid velocity and/or pressure (see e.g., Merin *et al.*, (1980) *J. Food Proc. Pres.* 4(3):183-198); creating turbulence in the feed channels (Blatt *et al.*, Membrane Science and Technology, Plenum Press, New York, 1970, pp. 47-97); pulsing the feed flow over the filter (Kennedy *et al.*, (1974) *Chem. Eng. Sci.* 29:1927-1931); designing flow paths to create tangential flow and/or Dean vortices (Chung *et al.*, (1993) *J. Memb. Sci.* 81:151-162); and using rotating filtration to create Taylor vortices (see e.g., Lee and Lueptow (2001) *J. Memb. Sci.* 192:129-143 and U.S. Pat. Nos. 5,194,145, 4,675,106, 4,753,729, 4,816,151, 5,034,135, 4,740,331, 4,670,176, and 5,738,792, all of which are incorporated herein in their entirety by reference thereto).

Taylor vortices are induced in the gap between coaxially arranged cylindrical members when the inner member is rotated relative to the outer member. Taylor-Couette filtration devices generate strong vorticity as a result of centrifugal flow instability ("Taylor instability"), which serves to mix the filtered material concentrated along the filter back into the fluid to be processed. Typically, a cylindrical filter is rotated within a stationary outer housing. It has been observed that membrane fouling due to concentration

polarization is very slow compared to dead-end or tangential filtration. Indeed, filtration performance may be improved by approximately one hundred fold.

The use of Taylor vortices in rotating filtration devices has been applied to separation of plasma from whole blood (see e.g., U.S. Pat. No. 5,034,135). For this application, the separator had to be inexpensive and disposable for one-time patient use. Further, these separators only had to operate for relatively short periods of time (e.g., about 45 minutes). Moreover, the separator was sized to accept the flow rate of blood that could reliably be collected from a donor (e.g., about 100 ml/minute). This technology provided a significant improvement to the blood processing industry. The advantages and improved filtration performance seen with rotating filtration systems (Taylor vortices) have not been widely exploited in other areas of commercial fluid separation.

In commercial blood separators, a fluid seal and mechanical bearings prevent the separated plasma from remixing with the concentrated blood cells. Pressure drives the plasma through the seal and mechanical bearings and into a tubing port that leads to a collection container. The rotor spins on an axis defined by two shaft bearings, one on either end. Spinning is induced by a rotating magnetic field and a magnetic coupling. A motor with permanent magnets fixed to its rotor generates the rotating magnetic field. While this design is appropriate for a disposable blood separator, it is not well adapted for long-term operation. First, the design adds a rotational drive motor to any filtration system, beyond the pump(s) needed for fluid feed and collection. Further, the seals are likely to wear out if the rotor is spun at 3600 rpm for prolonged periods. Likewise, the bearings that support the rotor are also likely to wear out. Use of seals and bearings adapted for continuous long-term use (like those used conventional pumps) are expensive and suffer from reliability concerns.

One other fluid separation technology, reverse osmosis (RO) membrane filtration, is well suited for removal of dissolved ions, proteins, and organic chemicals, which are difficult to remove using conventional filtration methods. Further, RO membrane systems are regenerable, thereby providing long term membrane service, requiring replacement only 1-2 times per year in commercial membrane plants. Moreover, because RO is an absolute filtration method, its treatment efficiency and performance are stable and predictable (Lee and Lueptow (2001) Reverse osmosis filtration for space mission wastewater: membrane

properties and operating conditions. *J. Memb. Sci.* 182:77-90). However, membrane fouling due to concentration polarization is still a problem in conventional RO filtration.

Lee and Lueptow recently published a study that suggests that rotating filtration devices that use Taylor vortices to reduce concentration polarization may be used to enhance filtrate flux through reverse osmosis (RO) membranes (Lee and Lueptow (2001) Rotating reverse osmosis: a dynamic model for flux and rejection. *J. Memb. Sci.* 192:129-143). Unfortunately, existing Taylor-Couette systems/devices, such as those discussed above with respect to blood separation, are poorly suited for large scale commercial applications where long-term continuous operation is desirable. Consequently, a need exists for energy efficient, rotating membrane filtration systems/devices, compatible with reverse osmosis membranes, adapted to long-term continuous use and scalable for commercial separation applications.

Summary of the Invention

Aspects of the present invention are directed to a device for rotational filtration. In one embodiment, the device comprises a housing having a bore with an inner wall. The housing has an inlet port for the flow of process fluid into the device and a filtrate port for the collection of filtrate. The housing may also have an outlet port for the flow of process fluid out of the device. The device also comprises a rotor having an outer wall. The rotor is adapted to rotate within the bore and has a rotational drive means adapted for driving the rotation of the rotor by the flow of process fluid. The device also comprises a filter attached to either the outer wall of the rotor or the inner wall of the bore.

In one preferred embodiment, the rotational drive means comprises a plurality of turbine vanes on the rotor. The turbine vanes are positioned at least partially within the flow path of the process fluid, to drive the rotation of the rotor. In one specific embodiment, the turbine vanes are positioned at the inlet port and the flow of process fluid into the device drives the rotation of the rotor.

According to another aspect of the present invention, the rotational filtration device also comprises a gap between the rotor and the housing, wherein the gap is configured so as to facilitate formation of Taylor vortices within the gap when the rotor is rotating within the bore. In one preferred embodiment the gap is sized so that the ratio of the gap to radius is

less than about 0.142. In other embodiments the gap is sized so that the ratio of the gap to radius is greater than about 0.142.

A filter is disposed within the gap. The filter is preferably provided in the form of a membrane for some embodiments. In one preferred embodiment, the membrane is attached to the inner wall of the bore. In another specific embodiment, the housing further comprises a layer of porous material located between the membrane and the inner wall.

According to yet another aspect of the present invention, the rotor further comprises surface modifications adapted to create wake turbulence. These surface modifications may include longitudinal grooves.

Preferably, the filter comprises a filtration membrane which is selected from the group including micro, macro, nano, dialysis and reverse osmosis membranes.

A method is disclosed in accordance with another embodiment of the present invention for filtering a solution and/or suspension to separate soluble and/or insoluble materials from a liquid filtrate. The method comprises the steps of: (1) providing a device comprising a cylindrical housing having at least one inlet port and at least one filtrate port, a cylindrical rotor adapted to rotate within the housing, the rotor having a rotational drive means comprising a plurality of turbine vanes, and a filtration membrane affixed to the rotor or the housing, between the at least one inlet port and the at least one filtrate port; (2) introducing the solution and/or suspension under pressure into the at least one inlet port, such that the solution and/or suspension flows across the turbine vanes causing the rotor to rotate within the housing; (3) allowing the rotor to rotate at a rate sufficient to generate Taylor vortices in a gap between the rotor and the housing, thereby reducing concentration polarization along the filtration membrane; and (4) collecting the filtrate from the at least one filtrate port after passing through the filtration membrane.

In accordance with another preferred embodiment, a filtration device is disclosed. The device comprises: a housing having a bore; an inlet port on the housing; a filtrate port on the housing; a rotor adapted to rotate within the bore, the rotor comprising a turbine vane configured to convert a flow of pressurized process fluid from the inlet port into rotational energy; a gap between an inner surface of the bore and the rotor; and a filter within the gap, between the inlet port and the filtrate port.

Brief Description of the Drawings

Figure 1 is a sectional view of the rotational filtration device according to one embodiment of the present invention.

Figure 2 is an enlarged view of the circled area in Figure 1 to show the gap between the outer wall of the rotor and the inner wall of the housing.

Figure 3 illustrates the end of the housing viewed along the central axis of the rotational filtration device.

Figure 4 is a cross sectional view of the rotational filtration device at line A-A' of Figure 1.

Figure 5a is a sectional view of the rotor taken along line B-B' of Figure 5b.

Figure 5b is cross sectional view of the rotor showing the turbine vanes.

Figure 6a is a sectional view of the rotor taken along line C-C' of Figure 6b.

Figure 6b is a cross sectional view of the rotor and turbine vanes.

Figure 7 illustrates a rotational filtration device according to another embodiment of the present invention, having one or more inner cylindrical sections added to the rotor.

Figure 8 illustrates an end view of a rotational filtration device having two inlet ports.

Detailed Description of the Preferred Embodiments

Figure 1 is a sectional view of the rotational filtration device 100 according to one embodiment of the present invention. The sectional view shows the housing 150 of the rotational filtration device bisected along line A-A', but the rotor 110 is shown intact. The rotational filtration device 100 comprises a rotor 110 arranged coaxially within the bore of a housing 150. In the illustrated embodiment both the rotor 110 and the bore are cylindrical. In one embodiment the rotor 110 is mounted on two posts 152 within the housing 150 along the central axis 102 of the rotational filtration device 100. These posts limit both the axial and the radial motion of the rotor 110. There is a gap 104 between the outer wall 112 of the rotor 110 and the inner wall 154 of the housing 150. The gap 104 extends evenly around the rotor 110. In another embodiment the posts 152 are not used and the rotor 110 is suspended within the housing 150 solely by the flow of process fluid through the gap 104.

The housing 150 comprises an inlet port 156 and one or more filtrate ports 158. The process fluid flows into the rotational filtration device 100 via the inlet port 156. The filtrate (filtered process fluid) flows out of the rotational filtration device 100 via the filtrate ports 158. Additionally, the housing 150 may comprise an outlet port (not shown), through which the process fluid flows out of the rotational filtration device 100. The outlet port allows the flow of process fluid through the rotational filtration device 100 at a greater rate than the flow of filtrate out of the rotational filtration device 100. The number of each port may be adjusted to modify the flow of the process fluid.

The rotor 110 comprises a rotational drive means 114 which is positioned at least partially within the flow path of the process fluid to drive the rotation of the rotor 110. In the illustrated embodiment, the rotational drive means 114 comprises a plurality of turbine vanes. These turbine vanes are positioned at the inlet port 156 and the flow of process fluid into the rotational filtration device 100 via the inlet port 156 drives the rotation of the rotor 110.

A filter 106 is disposed within the gap 104. In the illustrated embodiment, the filter 106 is mounted on the inner wall 154 of the housing 150. In another embodiment, the filter 104 may be mounted on the outer wall 112 of the rotor 110. For this embodiment, the inlet port 156 is relocated to direct the flow of the process fluid into the interior of the rotor 110 to accommodate the mounting of the filter 106 on the outer wall 112 of the rotor 110.

According to some embodiments, the filter comprises of a filtration membrane which is selected from the group including micro, macro, nano, dialysis and reverse osmosis membranes.

Figure 2 is an enlarged view of the circled area in Figure 1 to clarify the gap 104 between the outer wall 112 of the rotor 110 and the inner wall 154 of the housing 150. As discussed above with reference to Figure 1, the filter 106 is mounted on the inner wall 154 of the housing 150. Referring to Figure 2, the filter 106 may be supported by a sintered porous bed 160 or any other porous structure known in the art. In one embodiment the porous bed may be made of stainless steel. The porous bed 160 provides a foundation for the filter 106 to withstand the high pressure within the housing 150 (e.g. 1000 psi), while its porosity adds little resistance to the flow of the filtrate out of the filtrate port 158.

The gap 104 is sized to provide optimal shear and vorticity to the process fluid as it flows through the gap 104. In one embodiment, the rotor is 1" in diameter, 5" long, and the

gap 104 is 0.020". The rotor 110 spins at a rate of 3600 rpm in this embodiment. Rotor and housing configurations and gap dimension can be modified as described in Lee and Leuptow (2001) in order to optimize filtrate flux.

The dimensions of the various components of the rotational filtration device 100 described above can be scaled up and down depending on the application. For example, the rotational filtration device disclosed in Lee and Lueptow (2001) employs a relatively large gap (0.142") on a rotor 110 radius of 1", or a gap to rotor radius ratio of 0.142. Some embodiments may employ a much smaller gap to increase shear. Other embodiments may employ a larger gap to increase Taylor vorticity. Increasing the gap increases Taylor vorticity but reduces shear. Those of skill in the art can readily determine the optimal balance between Taylor vorticity and shear depending on the application. For example, excessive shear is preferably avoided in blood separators to minimize damage red blood cells or other desired blood components. However, for water treatment (e.g., desalination), shear damage is of less or no concern.

It is known from tangential filtration that the higher the shear the better the membrane filter performs, because shear reduces membrane clogging by diminishing concentration polarization. In tangential filtration, however, there is a limit to the effectiveness of shear in improving filtrate flux because the tangential flow is generated by pumping pressure, which can be limiting. The Taylor-Couette devices as modified in the present invention allow increased shear without increased pressure, because the shear is created by the rotation of the rotor 110 within the housing 150 and varies as discussed above with the size of the gap 104. In one preferred embodiment, the gap to radius ratio is about 0.040, or about 1/3 that taught by the Lueptow reference (about 0.142) cited above.

Figure 3 illustrates the end of the housing 150 viewed along the central axis 102 of the rotational filtration device 100. As discussed above with reference to Figure 1, the housing 150 comprises an inlet port 156 and one or more filtrate ports 158. Referring to Figure 3, an outlet port 162 is also shown.

Figure 4 is a cross sectional view of the rotational filtration device 100 at line A-A' of Figure 1. As discussed above with reference to Figure 1, the rotor 110 comprises a rotational drive means 114 which is positioned at least partially within the flow path of the process fluid to drive the rotation of the rotor 110. Referring to Figure 4, the rotational drive means 114 comprises a plurality of turbine vanes 116. These turbine vanes 116 are

positioned at the inlet port 156 and sculpted to capture the flow of process fluid into the rotational filtration device 100 via the inlet port 156, which drives the rotation of the rotor 110. Preferably, the process fluid is pumped at a relatively high flow rate and pressure (e.g., about 100-1000 mL/min for the dimensions discussed above with reference to Figure 2).

Figure 5a is a sectional view of the rotor 110 taken along line B-B' of Figure 5b, which is cross sectional view of the rotor 110 similar to that in Figure 4. Figure 6a is a sectional view of the rotor 110 taken along line C-C' of Figure 6b, which is a cross sectional view of the rotor 110 similar to that in Figure 5b, except the rotor 110 is rotated clockwise about one sixth of a rotation. Figure 6a illustrates the semicircular shape 164 of the vanes.

In accordance with one preferred embodiment, the rotor is preferably freely supported. There may be center limit posts extending from the housing on the axis of rotation. These limit posts restrict both axial and radial motion of the rotor until it reaches its optimal self-centering speed.

A rotor surrounded by a viscous fluid and constrained to rotate within a bearing surface will self-center itself. Fluid tends to follow the rotor, and thus the rotor is in a sense totally submerged as it spins. Pressure increases where the gap is small, and the pressure tends to push the rotor away from the case and increase the gap.

There are preferred ranges of rotational speed (RPM) where the self-centering effect becomes optimal. That RPM range depends on viscosity and density of the fluid, gap, rotor geometry, and possibly other variables. The center limit posts help keep the rotor reasonably centered during spin-up of the system.

In one preferred embodiment, as shown in Figures 5-6, the rotor includes a section of turbine vanes, centrally located under the tangential inlet port. Preferably, process fluid (salt water for example) is pumped at a relatively high flow rate for the system dimensions described above (e.g., about 100-1000 mL/min) and at high pressures. Figures 4-6 show some detail on the vanes. The inlet port is preferably positioned so that inlet flow hits the rotor tangentially in the form of a jet. The vanes are preferably sculptured to capture this inlet flow and convert it into rotational energy.

The self-centering forces described above with respect to a rotor surrounded by a viscous fluid operate to cause radial centering. Design features of the turbine vanes that

function to keep the rotor axially centered are illustrated in Figures 6a and 6b (see e.g., the cut-out 164 in Figure 6a, corresponding to the section C-C' in Figure 6b). The curvature of the vanes can be shaped to divert the forces of the inlet flow to move the rotor to a stable equilibrium position directly under the inlet port. Inlet flow against the semicircular shape of the vane will tend to split, with some going left and some going right. When the device is horizontal, as shown in Figure 6a and 6b, if the rotor moves to the right under the inlet port, the left wall of the vane 163 will accept more force than the right wall 165, and this will tend to move the rotor back to center it under the inlet port. This is an axial self-centering design feature. The vanes can be modified, as known to those of skill in the art, to stabilize the rotor so it levitates, in a sense, and does not contact either center limit post. For example, if axial flow of the feed fluid tends to push the rotor towards the outlet port, the curvature of the vane can be modified, making the curvature on the left side steeper than on the right. This will add a force to oppose that pushing the rotor to the outlet port.

In some embodiments the rotor 110 is solid. In other embodiments the rotor 110 is hollow. In some of these other embodiments the hollow rotor 110 is permeable to the process fluid to reduce the buoyancy of the rotor 110 within the housing 150.

Referring to Figures 1 and 2, the surfaces of the outer wall 112 of the rotor 110 and the inner wall 154 of the housing 150 may be modified to increase turbulence and enhance the formation of Taylor vortices. For example, texture may be added to either or both surfaces. More particularly, longitudinal grooves on the outer wall 112 of the rotor 110 will cast trailing wakes that will increase Taylor vorticity and should improve filtrate flux. Further, the addition of surface modifications such as longitudinal grooves may be used to create an exit path for the inlet flow, which is diverted to the right by the turbine vanes as illustrated in Figure 4. The exit path could be along deep longitudinal groves that direct flow from the right side of the housing 150 back into the gap 104 and then out through an outlet port 162.

Referring to Figure 4, the rotation of the rotor 110 coaxially within the housing 150 generates a self-centering effect. The rotor 110 behaves like a spinning shaft within a journal bearing, with the process fluid serving as a lubricant. The process fluid forms a sheet within the gap 104 between the rotor 110 and the housing 150. The rotation of the rotor 110 induces motion in the process fluid which produces a hydrodynamic pressure in the sheet. The hydrodynamic pressure is a function of the width of the gap 104, the

diameter of the rotor 110, its rate of rotation, the density and viscosity of the process fluid. Above a threshold rate of rotation, this hydrodynamic pressure tends to keep the width of the gap 104 even, causing the rotor 110 to self-center within the housing 150. Referring to Figure 1, the posts 152 keeps the rotor 110 reasonably centered along the central axis 102 before it reaches the discussed threshold rate of rotation. A more detailed discussion of the radial self-centering effect is given in the Standard Handbook for Mechanical Engineers, 7th Edition (1967), Baumeister and Marks, pages 156-157.

As discussed immediately above and earlier with reference to Figure 2, the width of the gap 104 affects shear, Taylor vorticity, and the hydrodynamic pressure which generates self-centering effect of the rotor 110. The optimization of any one of these factors may reduce the effect of the other two. One possible solution is discussed with reference to Figure 7.

Figure 7 illustrates a rotational filtration device built according to another embodiment of the present invention. One or more inner cylindrical sections 118 are added to the rotor 110 in the illustrated embodiment. In other embodiments these inner cylindrical sections 118 may be arranged within the length of the rotor 110. These inner cylindrical sections 118 cooperate with outer cylindrical sections 166 added to inner wall 154 of the housing 150, forming a gap 108 between them. The gaps 104 and 108 have different widths, allowing the gap 104 to be optimized for filtration (e.g., shear and Taylor vorticity) and the gap 108 to be optimized for self-centering the rotor 110 (e.g., hydrodynamic pressure).

While the inner cylindrical sections 118 have a smaller diameter than the rotor 110, and the outer cylindrical sections 166 are implemented as protrusions in the illustrated embodiment, another embodiment may implement the inner cylindrical sections 118 with a greater diameter than the rotor 110, and the outer cylindrical sections 166 as cooperating depressions. Further, the length of the rotor 110 and the cooperating inner cylindrical sections 118 and outer cylindrical sections 166 may be adjusted to modify the optimization effects.

Forces which tend to cause the rotor 110 to move off-center from the central axis 102 (see e.g., Figure 1) include the flow of the process fluid into and out of the housing 150 via the inlet port 156 as well as the flow of filtrate out of the housing 150 via the filtrate ports 158, and in some embodiments, via an outlet port 162, shown in Figure 8. The outlet

port may be used in some embodiments to re-circulate unfiltered process fluid that was used to drive the turbine, but could not be filtered without unduly increasing the filtration pressure. In one embodiment, the outlet port may include a valve, adapted to maintain a constant filtration pressure within the device, while providing sufficient fluid flow to drive the rotor at a desired RPM. To minimize the off-centering forces, the number of these ports (inlet, filtrate and outlet) may be adjusted.

Figure 8 illustrates a rotational filtration device similar to that discussed above with reference to Figures 1-6, but with two inlet ports 156. Generally, a rotational filtration device having a plurality of ports serving the same function (e.g., a plurality of inlet ports) will have those ports arranged evenly around the circumference of the housing 150. In the illustrated embodiment, the two inlet ports 156 are opposed such that their respective effect on the rotor 110 (not shown) is offset or balanced. In some embodiments, the respective flow of the process fluid into the housing 150 via each inlet port 156 may be individually adjusted to further tune the use of the two opposed inlet ports 156. In other embodiments, the number of outlet ports and filtrate ports may also be adjusted. The minimization of off-centering forces may reduce the necessary gap hydrodynamic pressure for the rotor 110 to self-center.

Table 1 summarizes the experimental results obtained using a motor-driven RO prototype system. The prototype rotational filtration device used a Hydranautics ESNA membrane (Oceanside, CA). Hydranautics calls this a nanofilter. The rotor was 1" in diameter, 5" long, and the gap was 0.020". Each housing half contained a 1.4" by 3.5" sheet of membrane (4.9 in^2 or 32 cm^2) covering a filtrate port. The reduction in active membrane area from its mounting on a porous bead diminished the active surface area by about 50%.

The rotor used in developing the data presented in Table 1 did not include the turbine drive vanes described above with reference to Figures 1-6. Instead, it was rotated via magnetic drive. Rotor speeds varied from 3000 to 4600 RPM. The test solution was NaCl (ordinary table salt) in tap water. Trans-membrane pressure ran between 50 and 160 psi.

Date of Experiment	Salt content input (ppm)	RPM	Pump used	Input flow (mL/min)	Pressure (psi)	Top half filter: Drip rate	Top half filter: Salt content	Top half filter: % rejection	Bottom half filter: Drip rate	Bottom half filter: Salt content	Bottom half filter: % rejection	Comments
4/4/2002	0	3000	Teel 1P777		100	10	0	NA	13	0	NA	running fresh water
					90	10	0	NA	14	0	NA	
					80	12	0	NA	17	0	NA	
					70	17	0	NA	22	0	NA	
					60	18	0	NA	24	0	NA	
					50	21	0	NA	29	0	NA	
4/4/2002	0	4000	"		90	10	0	NA	14	0	NA	running fresh water
					70	13.5	0	NA	18.5	0	NA	
					50	21	0	NA	29	0	NA	
4/5/2002	500	3000	"	30	90	8	200	60	13	0	100	
4/8/2002												New rotor and magnetic drive
4/8/2002	0	3000	"		90	6	0	NA	12	0	NA	running fresh water
					80	7	0	NA	13.5	0	NA	
					70	8	0	NA	16	0	NA	
					60	10	0	NA	18.5	0	NA	
					50	12	0	NA	21.5	0	NA	
4/8/2002	750	3000	"		90	7	200	73	11.5	0	100	
					90	8			11.5			
					90	10	300	60	15.5	100	87	
4/9/2002	1250	3000	"		95	7	700	44				
					90	8	700	44	18	500	60	
					80	9	600	44	16	400	68	
4/10/2002	2500	3000	"	5 (?)	95	11			21			
					95	12			22			
					95	10	1300	48	20.5	1000	60	
4/12/2002	5000	3000	"	5 (?)	95	10.5			21.5			
					95	15			29			
					95	14	6000	0	24.5	2500	50	By this time Top leaks significantly
4/12/2002	10000	3000	"		95	14	5000	50	24	4000	60	
					80	15	10000	0	29	3500	65	Top leaks and salt content = input
4/20/2002	0		Haldex 4F 649A	100	95	14	0	NA	21.5	0	NA	Switched to new pump & running fresh water
					120	10	0	NA	17	0	NA	
4/20/2002	10000	3000	"	100	100	25			60			
					120							
					140	12			28			
					160	10	10000	0	23	4500	55	Top leaks and salt content = input
4/21/2002	10000	4600	"	100	120	9			23			
					140	7			18			
					150	6			16.5			
					160	6			18			
4/21/2002		0	"	100	160	6			16			Filtrate flow rate same with rotor stationary

Table 1

Table 1 shows that up to 100% of the salt contaminating the feed solution was rejected. These results clearly suggest that placing the membrane on the housing is acceptable, and that salt can be removed from water at relatively low pressures and rpm.

In variations to the embodiment illustrated in Figures 1-8, this invention can be applied to a vast number of applications. In a general sense, embodiments of this invention can be useful in any application where filters loose performance due to clogging or concentration polarization. These applications include: removal of salt from water, processing sea water for human consumption, processing sea water for agricultural uses, reprocessing waste water for agricultural uses, reprocessing waste water for human consumption, concentrating sugar or other desired components from sap from plants, such as sugar cane sap or maple sap, concentrating latex from the sap of rubber plants, removing impurities from water for industrial applications, such as needed in the pharmaceutical or electronic industries, recycling cooking oil, recycling motor oil or lubricating oils, and producing sterile water for intravenous injection.

Further, where molecular exclusion or sieving membranes are employed, the device can be used for large scale cell and biotechnology separation applications, such as purifying cell supernatants and/or lysates from cellular material in a bioprocessor or fermentor. The advantages discussed above with regard to energy efficiency (flow-driven turbine) and high flux rates (vortex-scrubbed membranes) would be applicable to the large scale filtration needs of the biotechnology industry. Similarly, some embodiments of the present turbine-driven device may be well suited for energy-efficient filtration of fermented beverages, to remove for example, yeast and particulate material (grains, vegetable matter, fruit, etc.) in the production of wines and beers.

The various materials, methods and techniques described above provide a number of ways to carry out the invention. Of course, it is to be understood that not necessarily all objectives or advantages described may be achieved in accordance with any particular embodiment described herein. Thus, for example, those skilled in the art will recognize that the components of the system may be made and the methods may be performed in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other objectives or advantages as may be taught or suggested herein.

Although the present invention has been described in terms of certain preferred embodiments, other embodiments of the invention including variations in dimensions, configuration and materials will be apparent to those of skill in the art in view of the disclosure herein. In addition, all features discussed in connection with any one embodiment herein can be readily adapted for use in other embodiments herein. The use of different terms or reference numerals for similar features in different embodiments does not imply differences other than those which may be expressly set forth. Accordingly, the present invention is intended to be described solely by reference to the appended claims, and not limited to the preferred embodiments disclosed herein.

WHAT IS CLAIMED IS:

1. A device for rotational filtration, comprising:

a housing having a bore with an inner wall, said housing also having an inlet port for directing a flow of pressurized process fluid into the device and a filtrate port for collecting a filtrate;

a rotor having an outer wall, and being adapted to rotate within said bore, said rotor also having a rotational drive means for converting the flow of pressurized process fluid into rotational energy; and

a filtration membrane attached to either said rotor or said inner wall of said bore.

2. The device of claim 1, wherein said rotational drive means comprises a plurality of turbine vanes on said rotor, said turbine vanes being positioned at least partially within a flow path of the pressurized process fluid.

3. The device of claim 1, further comprising a gap between said rotor and said housing, wherein said gap is configured so as to facilitate formation of Taylor vortices within the gap when said rotor is turning within said bore.

4. The device of claim 3, wherein said gap is sized so that the ratio of gap to radius is less than about 0.142.

5. The device of claim 1, wherein said filtration membrane is attached to said inner wall of said bore.

6. The device of claim 5, further comprising a layer of porous material located between said filtration membrane and said inner wall.

7. The device of claim 1, wherein said rotor further comprises surface modifications adapted to create wake turbulence.

8. The device of claim 7, wherein said surface modifications are longitudinal grooves.

9. The device of claim 1, wherein said filtration membrane is selected from the group consisting of micro, macro, nano, dialysis and reverse osmosis membranes.

10. The device of claim 1, wherein said rotor is radially self-centering.

11. The device of claim 2, further comprising at least two inlet ports arranged at equal circumferential distances from one another, wherein the flow of pressurized process

fluid against the turbine vanes on said rotor improves radially self-centering at a lower RPM.

12. The device of claim 2, wherein said turbine vanes are shaped so as to allow said rotor to axially self-center within the flow path.

13. A method for filtering a solution and/or suspension to separate soluble and/or insoluble materials from a liquid filtrate, comprising:

providing a device comprising a cylindrical housing having at least one inlet port and at least one filtrate port, a cylindrical rotor adapted to rotate within said housing, said rotor having a rotational drive means comprising a plurality of turbine vanes, and a filtration membrane affixed to said rotor or said housing, between said at least one inlet port and said at least one filtrate port;

introducing the solution and/or suspension under pressure into said at least one inlet port, such that the solution and/or suspension flows across the turbine vanes causing the rotor to rotate within the housing;

allowing said rotor to rotate at a rate sufficient to generate Taylor vortices in a gap between said rotor and said housing, thereby reducing concentration polarization along the filtration membrane; and

collecting the filtrate from the at least one filtrate port after passing through the filtration membrane.

14. A filtration device, comprising:

a housing having a bore;

an inlet port on said housing;

a filtrate port on said housing;

a rotor adapted to rotate within said bore, said rotor comprising a turbine vane configured to convert a flow of pressurized process fluid from said inlet port into rotational energy;

a gap between an inner surface of said bore and said rotor; and

a filter within said gap, between the inlet port and the filtrate port.

15. The filtration device of Claim 14, further comprising an outlet port.

16. The filtration device of Claim 15, wherein said outlet port comprises a valve adapted to maintain a constant filtration pressure.

17. The filtration device of Claim 14, wherein a ratio of said gap to a diameter of said rotor is less than about 0.142.

18. The filtration device of Claim 14, wherein a ratio of said gap to a diameter of said rotor is about 0.04.

19. The filtration device of Claim 14, wherein a ratio of said gap to a diameter of said rotor is about 0.02.

20. The filtration device of Claim 14, wherein an external surface of said rotor additionally comprises a plurality of longitudinal groove.

21. The filtration device of Claim 14, wherein said filter comprises a reverse osmosis membrane.

22. The filtration device of Claim 14, wherein a diameter of said rotor varies along a length of said rotor such that said gap varies in width.

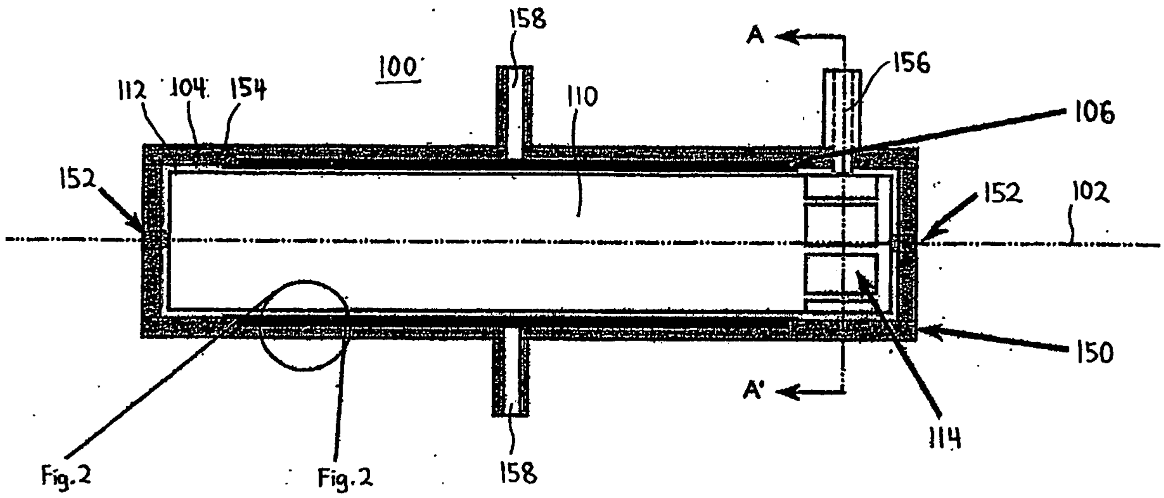
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Fig.2
Fig.2
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Fig. 1

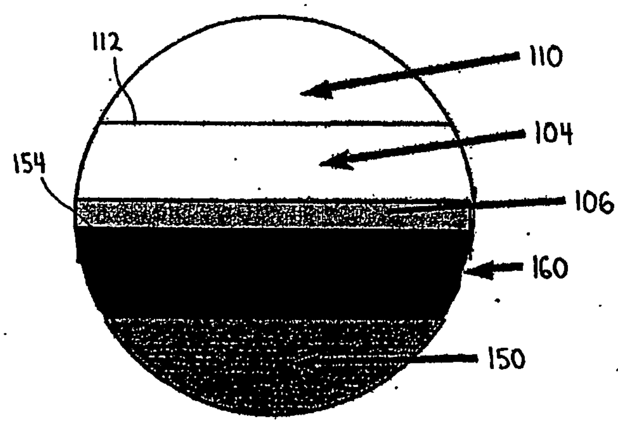
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Fig. 2

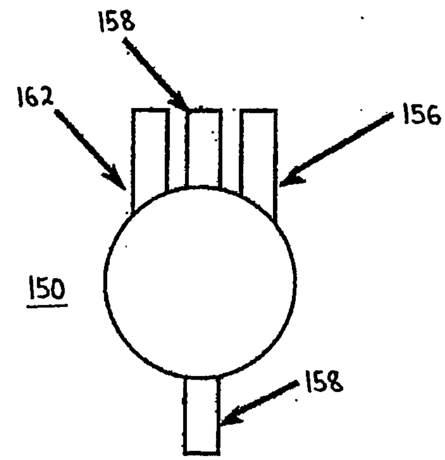

Fig. 3

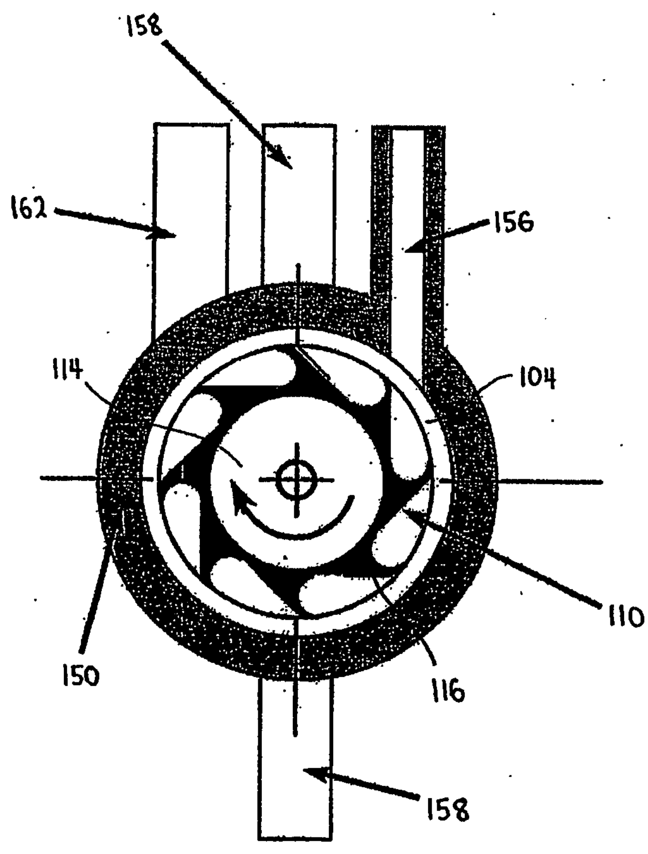

Fig. 4

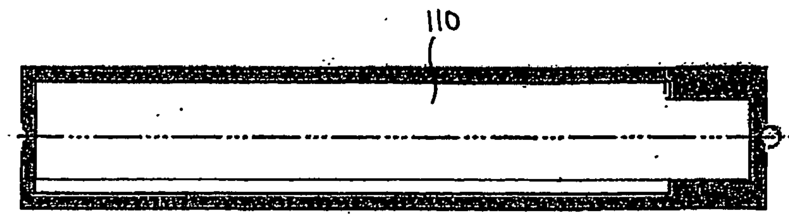

Fig. 5a

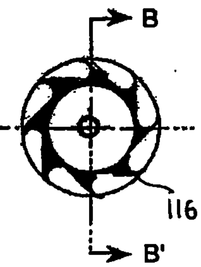

Fig. 5b

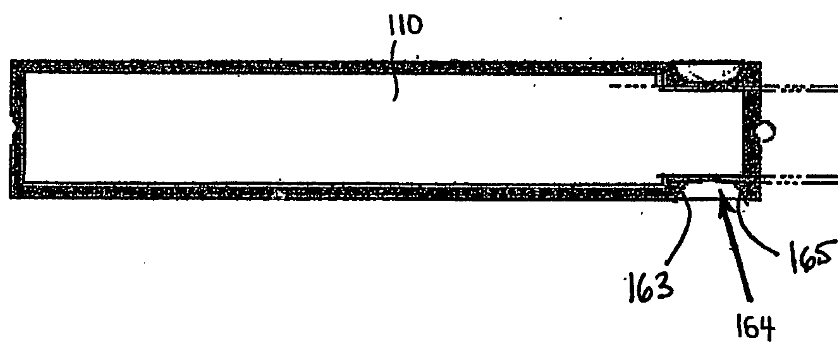

Fig. 6a

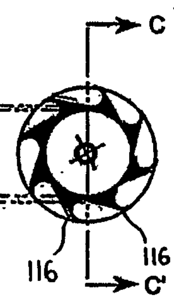

Fig. 6b

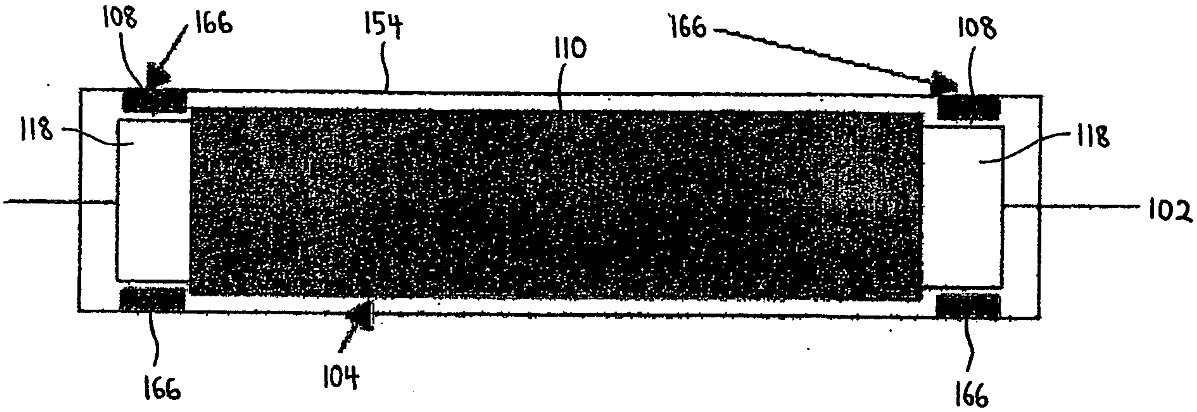
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Fig. 7

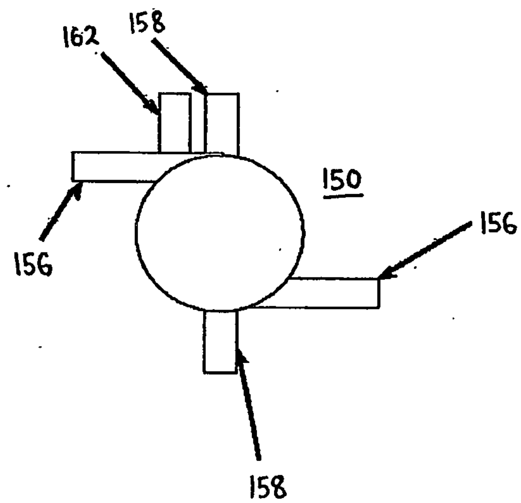
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Fig. 8

INTERNATIONAL SEARCH REPORT	International application No. PCT/US03/16894

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : B01D 29/00,33/00, 61/00, 63/00; C02F 1/00; B04B 11/00

US CL : 210/350,354,784,650,297,321.84,321.75,323.2,324,326,179,780; 494/5,24,28,29,30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 210/350,354,784,650,297,321.84,321.75,323.2,324,326,179,780; 494/5,24,28,29,30

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 6,210,311 B1 (MAY) 03 April 2001 (03.4.2001) abstract, figures and entire text	1-3, 11, 13,14, 15 — 4-8,16-19
X — Y	US 3,879,294 A (ELLIS et al) 22 April 1975 (22.4.1975) abstract, figures and entire text	1-3, 11, 13,14, 15 — 4-8,16-19
Y	US 4,448,688 A (HAVLIS) 15 May 1984 (15.5.1984) abstract, figures,	1-3, 13-15
Y	US 5,900,142 A (MALONEY, Jr. et al) 04 May 1999 (04.5.1999) abstract, figures, col 2 line 50 - col 4 line 33	1-12, 13-22
A	US 5,906,733 A (PURVEY) 25 May 1999 (25.5.1999) Abstract, figures and the specification	1-12, 14-22
Y	US 5,738,792 A (SCHOENDORFER) 14 April 1998 (14.4.1988) figures, abstract, columns 3-5	1-12, 14-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search 22 July 2003 (22.07.2003)	Date of mailing of the international search report 03 SEP 2003
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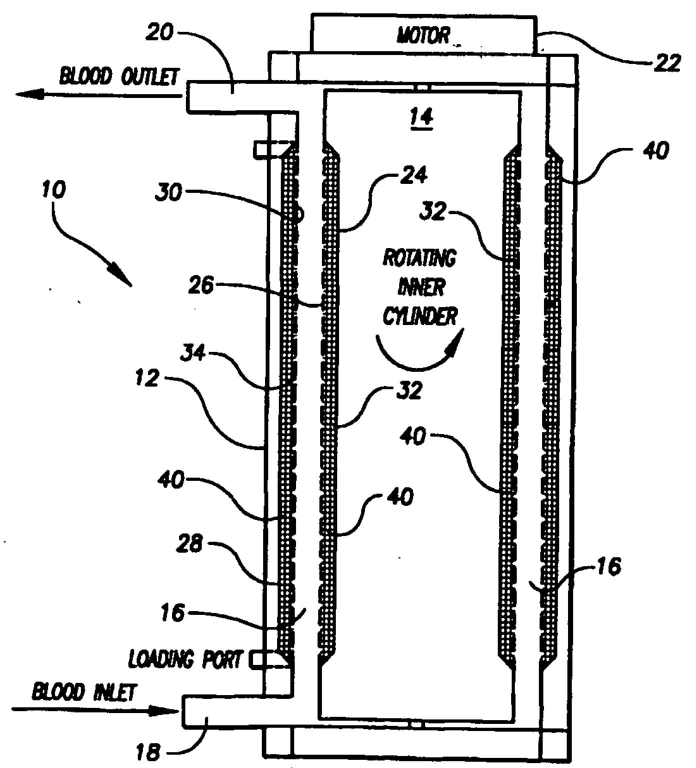
(54) Title: APPARATUS AND METHOD FOR TREATING WHOLE BLOOD

(57) Abstract

Apparatus for removing substances from blood. The apparatus includes concentric cylinders defining an annulus therebetween with the inner cylinder adapted for rotation with respect to the outer cylinder. At least one of the cylinders includes a porous membrane covered portion forming a compartment containing an immobilized active species. The active species is adapted to break down or remove the substance. Plasma in blood flowing in the annulus passes through the porous membrane and interacts with the active species either by reaction or binding. Red and white blood cells do not pass through the membrane. In this way, a substance is removed from plasma without exposing blood cells to the active species.



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APPARATUS AND METHOD FOR TREATING WHOLE BLOOD

This application claims benefit and priority of U.S. Provisional Applications 60/066,017 and 60/066,018, both filed November 14, 1997, both of which are incorporated by reference herein.

Background of the Invention

This invention relates to apparatus and method for removing substances such as drugs and toxins from whole blood.

The incidence of end-stage renal disease (ESRD) in the United States exceeds 200 per million population and continues to rise by approximately 8% per year, largely with the inclusion of elderly hypertensive and/or diabetic patients (see, for example, "Morbidity and Mortality of Dialysis," NIH Consensus Development Conference Statement, November 1-3, 1993, **11**:1-33). The treatment of choice for ESRD is kidney transplant. However, the limited number of donor organs, presence of qualifying co-morbidities, and low transplant rate for the elderly, ensures that hemodialysis will remain the primary method of renal replacement therapy in the foreseeable future. By the turn of the century, nearly 390,000 patients are expected to be enrolled in dialysis programs.

It is often necessary or desirable to remove substances from blood without damaging the cells contained within whole blood. An example is the desirability of removing the anticoagulant heparin from blood before the blood is returned to a dialysis patient. A well known enzyme, heparinase, reacts with heparin causing it to break down. Unfortunately, heparinase immobilized on solid supports is unsuitable for use with prior art bioreactors to remove heparin from blood, because the solid supports cause hemolysis in whole blood. A goal has been to design a bioreactor which would allow the clinical use of enzymes such as heparinase in a safe and efficient manner with whole blood. Conventional membrane reactors (hollow fibers) have the disadvantage of reduced mass transfer to a reactive membrane and therefore surface area of contact has to be maximized often resulting in infeasible devices. Fluidized beds of, for example, agarose beads result in good mass transfer but the fluid dynamics of the particles in blood can lead to hemolysis of the red cells and packing of the beads will occur at high flow rates.

Another substance which it is highly desirable to remove from the blood of dialysis patients is β_2-microglobulin, which has been implicated in dialysis related amyloidosis (DRA). DRA is a severely debilitating, potentially life-threatening, and inevitable consequence of long-term hemodialysis. It is characterized by amyloid deposits preferentially in osteoarticular locations. The clinical sequela includes chronic pain, carpal tunnel syndrome, joint deformities, destructive arthropathy, cystic bone lesions, fractures, and spondylarthropathy. The incidence and severity of DRA increases with the length of dialysis therapy, reaching 70% after 10 years and 100% after 20 years. Further information about DRA can be found in Drueke, *et al*, "Dialysis-associated amyloidosis," *Advan. Renal Replac. Therapy* (1995) **2**:24-39, and Schaeffer *et al*, "Pathogenetic and diagnostic aspects of dialysis-related amyloidosis," *Nephrol. Dial. Transplant* (1995) **10**(Suppl 3):4-8. DRA is the most incapacitating consequence of long-term dialysis and remains *inescapable*.

In the absence of established methods to treat or avoid DRA, interventions are limited to merely symptomatic relief. Patients are typically on chronic pain management with variable efficacy. Low-dose steroids relieve some of the symptoms but often have intolerable side-effects. Numerous orthopedic procedures are the rule, including carpal tunnel surgery, arthroscopic synovectomy, bursectomy, cyst curettage and filling, tendon sheath and ligament resections, and others. For advanced destructive arthropathy, prosthetic replacements of weight-bearing joints, such as the hips, are commonly necessary. In patients with destructive spondylarthropathy associated with spinal cord or nerve-root compression, orthopedic consolidation may constitute a life-saving procedure. Conservative and approximate estimates of the cost to treat the complications of DRA exceed $500 million/year.

Although the mechanisms of DRA development are under investigation, it is certain that retention of β_2M, the precursor molecule of the amyloid fibrils, is an absolute prerequisite. β_2M is a non-polymorphic single chain polypeptide (11,800 Mw) that is continually shed from cell membranes. It is a noncovalently-bound subunit of the class I Major Histocompatibility Complex. It accumulates in renal failure primarily due to diminished excretion; it has been estimated that normal kidneys remove 150 mg of β_2M per day. Typical β_2M levels in normal adults are in the range of about 1-3 mg/l blood, while renal failure levels may reach or exceed 60

mg/l blood. Chronically elevated levels of β_2M must be present for DRA to occur. This causal role is further supported by demonstrations that measures effective at reducing the supply of β_2M can slow or halt disease progression and improve symptoms. These findings strongly support the development of a system able to re-establish and maintain normal levels of β_2M with the efficiency currently only achievable with a normally functioning kidney.

Conventional hemodialysis systems, which consist of a regenerated cellulosic membrane (cuprophane), do not remove β_2M. Although inexpensive, this membrane is impermeable to proteins, such as β_2M, resulting in a progressive accumulation of this protein. Therefore, research efforts have focused on modifying the dialysis technique to lower circulating β_2M levels, in the hope of favorably impacting the occurrence rate and course of this disease.

The use of highly permeable, synthetic dialysis membranes, such as polyacrylonitrile (AN69) and polysulfone (F60) have been shown to lower levels of β_2M, especially when used in conjunction with hemofiltration or hemodiafiltration. Although substantial reductions can be attained, β_2M removal is still incomplete and accumulation of the remaining protein continues to contribute to the pathophysiology of DRA. An additional concern with these systems is the indiscriminate removal of other middle weight molecules, such as hormones and growth factors. Given the performance limitations, these dialyzers are prohibitively expensive for use in a government regulated, capitated system, such as hemodialysis.

Hemoperfusion methods involving extracorporeal adsorption columns have also been used in conjunction with synthetic membrane hemodialysers to remove β_2M. The most developed of these is the BM-01 column containing a hexadecyl alkyl compound which has recently been tested in small groups of patients. Although superior to high-flux hemodialysers alone, protein accumulation still occurs, making the expense of this combination approach impractical. This column also requires a large priming volume, which may complicate the dialysis management of cardiovascularly tenuous patients, particularly since adsorption columns tend to have a high pressure drop along the length of the column. Further, this treatment has been found to induce hypotension, a reduction in hematocrit and platelet count, and the loss of beneficial plasma proteins (mainly lysozyme). Other adsorbents that have been

studied *in vitro* include collagen, gelatin, and various ligands. However, non-specific binding remains a concern with these approaches as none of them is geared specifically toward reduction of β_2M level.

Immunoadsorption approaches are attractive for their superior specificity and affinity as was demonstrated with the application of high-performance immunoaffinity chromatography to the removal of β_2M. Unfortunately, this system is not compatible with whole blood and requires plasma separation by filtration or centrifugation before the treatment can be applied. This is not a reasonable procedure to impose on patients already debilitated by extensive chronic interventions. An alternative immunoadsorption method is the immunoaffinity column in which antibodies are immobilized onto insoluble supports. This system is also unusable with whole blood. Furthermore, the flow velocity through packed columns is limited, resulting in a relatively slow removal process. The development of hemocompatible immunoadsorbents from conventional hemodialyzers has also been proposed. Although a bifunctional device has obvious appeal, the design limitations of this technology make it inadequate for this application. The dialyzers offer a finite, and relatively small, surface area for antibody immobilization, which is most suited for removing circulating compounds present in low concentrations. This would not be sufficient to counterbalance the 1,400-2,000 mg of β_2M generated weekly. In addition, compared to traditional particulate matrices, antibody binding to cuprophan-based dialyzers is less stable. Therefore, a large amount of ligand is required to achieve satisfactory immobilization. This also presents concerns of antibody shedding into the circulation, deteriorating binding capacity of the system, and a potential for unwanted immunological side effects. The modified dialyzers also have decreased clearance values and increased ultrafiltration coefficients. The performance limitations and cost of these systems have remained substantial obstacles to their establishment as common clinical modalities.

Pharmacological interventions are also being explored. Low molecular weight anionic sulphonate and sulphate compounds designed to interfere with amyloid - basement membrane interactions show promise in the animal model of familial amyloidosis, although the relevance to DRA has not been investigated. In addition,

aminoguanidine, which prevents the glycation of β_2M thought important in amyloidogenesis, is also being considered.

There is currently no renal replacement strategy that can achieve the same efficiency of β_2M removal as a normally functioning kidney. However, the approaches attempted thus far have provided invaluable information regarding the clinical benefits of even a partial reduction in protein load. The favorable impact on the onset and course of DRA supports the development of a system able to re-establish and maintain normal levels of β_2M.

It is an object of the present invention to provide a bioreactor capable of removing heparin, β_2M, or other substances from plasma with minimal or no damage to blood cells. This and other objects are achieved by the apparatus and methods described and claimed hereinbelow.

Summary of the Invention

The present invention utilizes the principle of simultaneous separation and reaction within the same device to achieve a high efficiency detoxification or purification process without compromising delicate components of the feed such as the blood cells in whole blood. The apparatus of the invention achieves plasma separation and the treatment of whole blood continuously without concentrating the cells, which could lead to hemolysis and clotting.

In one aspect of the invention, an apparatus for removing unwanted substances from blood includes concentric outer and inner cylinders defining an annulus therebetween. The inner cylinder is adapted for rotation with respect to the outer cylinder. At least one of an inner surface of the outer cylinder or an outer surface of the inner cylinder includes a porous membrane covered portion forming a compartment containing an immobilized species, the species adapted to remove the unwanted substance. An inlet is provided for introducing whole blood into the annulus for flow along the cylinders. An outlet port is provided for discharging the blood and the porous membrane allows plasma within the blood to interact with the immobilized species. The immobilized species may comprise, for example, antibodies, antibody fragments, catalytic antibodies, enzymes, peptides, proteins, or living cells.

In one embodiment, the inner surface of the outer cylinder, and/or the outer surface of the inner cylinder, include a recess covered by a mesh to exclude the immobilized species, the recess acting as a collection chamber for plasma after interaction with the immobilized species. This embodiment may further include a pump for circulating plasma from the recess back into the annulus.

According to the invention, rotation of the inner cylinder above a critical angular velocity generates Taylor vortices in the annulus, the vortices creating oscillatory pressure gradients within the annulus. These pressure gradients cause periodic undulations in the unsupported porous membrane, resulting in circumferential flow in the compartment containing the immobilized species which increases the activity of the immobilized species. In a preferred embodiment, the inner cylinder is caused to rotate via magnetic coupling to an external electric motor. A suitable rotation rate is 1200 r.p.m.

In a preferred embodiment, the active species is immobilized on beads, which may comprise, for example, agarose, cellulose, or protein A. These beads may be fluidized by the undulations of the porous membrane, increasing the activity of the immobilized species. Alternatively, the active species may be organized into micelles. In one such embodiment, the substance to be removed is heparin and the immobilized species is heparinase. In another embodiment, the unwanted substance is β_2-microglobulin and the immobilized species comprises antibody fragments. An apparatus for the removal of β_2-microglobulin may be adapted to remove as much as 0.2 g of β_2-microglobulin in a three-hour treatment, or preferably as much as 0.5 g of β_2-microglobulin in a two-hour treatment. Active volumes may be low, for example, 350 ml, 200 ml, or even 50 ml. Transmembrane flow rates in the reactor may be as high as 50 ml/min, 100 ml/min, or even 200 ml/min.

In yet another embodiment of the invention the apparatus is used for efficient and continuous plasmapheresis and no active immobilized species is required.

In a related aspect, the invention includes methods of collecting platelets from whole blood. A bioreactor similar to the one described above is provided, the bioreactor having at least two membranes to define three reaction chambers. The first membrane is adapted to pass platelets and plasma, but not larger blood cells, and the second membrane is adapted to pass only plasma. Platelets can then be continuously

removed from the center chamber, while the blood cells in the main reactor chamber and the plasma in the outermost chamber are remixed and returned to the patient.

In another aspect, the invention includes methods of removing substances from whole blood. The methods are characterized by continuous isolation and reintroduction of plasma into a whole blood flow, wherein the plasma is treated to remove substances while isolated from the blood cells. In one embodiment of this aspect of the invention, a bioreactor similar to that described above may be used. The substances to be removed may be unwanted toxins, or desired substances which are collected for later use. For example, the invention may be used to collect a desired species from a transgenic animal which has been engineered to secrete that species in its blood, or the invention may be used for platelet collection.

It will be appreciated by those skilled in the art that the novel bioreactor design disclosed herein may also have utility for treatment of nonbiological slurries and mixtures. The reactor of the invention may be used for a variety of applications wherein it is desired to continuously separate a slurry or mixture, treat one component thereof, and recombine the components. This may be desirable either when the solid component is fragile or reactive, as with whole blood, or when the active species is subject to damage from the solid phase, as in certain catalysis systems.

As the terms are used herein, priming volume is considered to be the volume of the reactor occupied by red blood cells, *e.g.*, the volume of the annular region of the reactor described above. The volume of the portion of the reactor in which the active species is contained is termed the active volume, and the total of the two represents the reactor volume.

Brief Description of the Drawing

Fig. 1 is a cross sectional view of a schematic illustration of the vortex flow plasmapheretic reactor of the invention.

Fig. 1a is a magnified portion of Fig. 1 illustrating Taylor vortices.

Fig. 2 is a cross sectional view of a bioreactor of the invention including a plasma pump.

Fig. 3 is a cross sectional view of an embodiment of the invention including a double pump head for plasmapheresis.

Fig. 4 is a cross sectional view of an embodiment of the invention being used for platelet collection.

Fig. 5 is a schematic diagram illustrating the use of the bioreactor of the invention in a dialysis setting.

Fig. 6 is a graph of the performance of the vortex flow plasmapheresis reactor of Example 1 in saline.

Fig. 7 is a graph of heparin versus time at the reactor inlet and reactor outlet in the live sheep experiment of Example 2.

Fig. 8 is a graph showing the percent conversion versus time for a single pass conversion in saline in the live sheep experiment of Example 2.

Fig. 9 is a graph of whole blood recalcification time versus time for a inlet and outlet whole blood recalcification times for immobilized heparinase reactor in the live sheep experiment of Example 2.

Fig. 10 is a graph of percent conversion versus time for immobilized heparinase reactor in the live sheep experiment of Example 2.

Fig. 11 is a graph of cell count versus time illustrating reactor blood compatibility data for sheep.

Fig. 12 is a graph of total protein versus time during an excorporeal procedure with the immobilized heparinase reactor in the live sheep experiment of Example 2.

Fig. 13 is a graph of whole blood recalcification time versus time for inlet and outlet heparin levels for immobilized heparinase reactor in the live sheep experiment of Example 2.

Fig. 14 is a graph of cell count versus time illustrating reactor blood compatibility data for sheep.

Fig. 15 is a graph of total protein versus time in a sheep experiment.

Fig. 16 is a graph of percent conversion versus time in an experiment with sheep.

Fig. 17 is a graph of heparin effect versus time in a membrane reactor using sheep blood.

Fig. 18 is a graph of the performance of the vortex flow plasmapheresis reactor of Example 3 with human blood *in vitro*.

Description of the Preferred Embodiment

With reference to Figs. 1 and 1a, a vortex flow plasmapheretic reactor 10 of the invention includes an outer cylinder 12 and a concentrically mounted inner cylinder 14. The concentrically mounted cylinders 12 and 14 define an annular chamber 16. A blood inlet 18 allows blood to flow into and along the annular chamber 16 and is discharged through a blood outlet 20.

The inner cylinder 14 is mounted for rotation within the outer cylinder 12. It is preferred that the inner cylinder 14 rotate by magnetic coupling with an external motor 22. That is, the motor 22 will contain magnets (not shown) which couple to magnets (not shown) on the top portion of the rotating inner cylinder 14. A preferred rotation rate for the inner cylinder 14 is about 1200 r.p.m.

In this embodiment, the inner cylinder 14 includes a recess 24 which may be formed by grooves covered by a porous membrane 26. Similarly, the outer, fixed cylinder 12 includes a recess 28 covered by a porous membrane 30. It is preferred that the outer and inner cylinders 12 and 14 be made of polycarbonate which is compatible with blood. It is also preferred that the porous membranes 26 and 30 be flexible polycarbonate or polyestercyclopore membranes having pore sizes in the range of 0.2-3 μm.

The recess 24 in the inner rotating cylinder 14 covered by the porous membrane 26 creates a compartment 32 which contains an active immobilized species. Similarly, the recess 28 in the outer cylinder 12 covered by the porous membrane 30 creates a compartment 34 also for containing an active immobilized species. As an example, an active species such as heparinase may be immobilized on agarose beads 40 contained within the compartments 32 and 34. As will be appreciated by those skilled in the art, an active species such as heparinase may be immobilized on agarose by first activating the agarose surface. The desired active enzyme or protein is then added. After a suitable period of time, the agarose beads containing the active species are thoroughly washed. While this specification uses heparinase as an example of an active species, it is to be understood that the invention is not limited to this enzyme. The invention comprehends the use of any active species which can interact chemically or physically with a component in blood. In particular, it is noted that the compartments 32 and 34 may include living cells for

interacting with components in blood thereby allowing the reactor to act, for example, as an artificial liver. In another example, the compartments may include antibodies or antibody fragments for removal of specific proteins and compounds such as β_2M. The active species may be immobilized by being bound to a solid support, or by containment within an ultrafiltration membrane. In the latter approach, it may be advantageous for the active species to be organized into micelles, for example by incorporation of a hydrophobic group into the species. In this embodiment, the active species should organize itself into micelles with the hydrophobic component at the center and the active region at the surface of the micelle.

According to the invention, the porous membranes 26 and 30 have pores selected to prevent the passage of blood components such as red and white blood cells but which allow plasma to pass through.

When the inner cylinder 14 rotates with respect to the fixed outer cylinder 12 at a speed above a critical rotation rate, Taylor vortices 42 (Fig. 1a) are generated in the annulus 16. These vortices 42 aid in the flow of plasma into the compartments 32 and 34 so that the plasma can interact with an active species immobilized on the beads 40. It is believed that the Taylor vortices also generate oscillating pressure gradients within the annulus 16 and these pressure gradient cause periodic undulations in the flexible porous membranes 26 and 30. The undulations in a circumferential direction result in circumferential flow in the compartments 32 and 34 containing the immobilized active species. The periodic undulations of the porous membranes are similar to peristalsis and are promulgated or transferred into the fluid in the active compartments. The Taylor vortices and induced circumferential flow create fluidization of the agarose immobilized species which minimizes mass transfer limitations in the compartments 32 and 34. The presence of Taylor vortices can be predicted by the value of a characteristic Taylor number, which is a function of system dimensions, cylinder rotation rate, and fluid properties.

In this example, heparin in the plasma portion of whole blood interacts with the immobilized heparinase and is broken down so that blood exiting through the blood outlet 20 will have substantially reduced levels of heparin. The fluidization of the immobilized species retards plasma clotting in the apparatus 10 and improves mass transfer rates in the reactor.

The periodic undulations of the porous membranes which create circumferential flow in the active compartments also minimize concentration polarization at the membrane surface, thereby allowing better performance of the plasma separation process, resulting in longer device operation times at higher filtration fluxes. Experiments in sheep have been run for as long as 5 hours with filtration fluxes of 50 ml plasma per minute. Other mechanisms which produce the membrane undulations (e.g., parametric pumping, membrane vibration) will achieve a similar result of enhancing mass transfer into the active volume and minimization of concentration polarization at the membrane.

With reference now to Fig. 2, an embodiment is shown with an additional recess 50 covered by a polyester mesh 52. The recess 50 will collect plasma while the polyester mesh 52 will prevent any of the immobilized active species from entering the recess 50. A plasma pump 54 transports plasma from the recess 50 and returns it at a return port 56. It is important that the treated plasma be returned directly into the device 10 either close to the whole blood outlet port (preferably) or close to the whole blood inlet port. Such a configuration eliminates concentration of cells which would precipitate clogging of the porous membrane 30. It is an added benefit that the return of the treated fluid near the whole blood inlet is able to dilute the feed thereby decreasing the hematocrit only within the device and not the patient. A lowered hematocrit in the apparatus will allow higher filtration fluxes. As in the embodiment of Fig. 1, the membrane 30 is located on the outer cylinder and is supported only at the top and bottom. The membrane is thus able to induce circumferential flow in the active compartment 34 though periodic undulations that arise from the fluid dynamics created by the rapid rotation of the inner cylinder.

Another embodiment of the invention is shown in Fig. 3. In this embodiment, there is no active species immobilized in the chamber 34. Rather, untreated plasma is withdrawn from the recess 50 and discharged. The pump 54 is double pump head and introduces saline from a saline reservoir 58 back into the device 10. The design of Fig. 3 ensures constant fluid balance within the device, minimizing concentration of cells due to the filtration process and preventing premature clogging of the membrane.

Still another embodiment of the invention is shown in Fig. 4. In this embodiment, the reactor comprises two flexible permeable membranes 58 and 60. The first membrane 58 has a relatively large pore size on the order of 5 μm, while the second membrane has a smaller pore size on the order of less than about 2 μm. Thus, the first membrane will pass plasma and platelets, which have a size of about 2-4 μm, while the second membrane will pass only plasma. Main chamber 16 will then contain large blood components such as red and white blood cells, middle chamber 62 will contain platelets, and outermost chamber 64 will contain plasma. The vortex flow reactor and the undulations of the membranes ensure that plasma circulates quickly throughout the system and that clotting is minimized.

It should be noted that in the embodiments shown in Figs. 1 and 2 the active species itself can be contained within the active compartments using a microporous membrane or an ultrafiltration membrane. The latter thus would eliminate the need to use a macroscopic polymeric support such as agarose. That is to say, by using an ultrafiltration membrane, heparinase itself could be contained in the active compartments without being immobilized on a substrate. In still other embodiments, multiple compartments of active materials may be provided, through which plasma passes either in series or in parallel. Alternatively, multiple immobilized active species may be provided within a single compartment.

In operation, (see Fig. 2) blood enters the apparatus 10 through a tangential bottom port 18 and flows upwardly through the annulus where blood plasma (which contains the substance to be modified or removed) is able to permeate the membranes and come into contact with the immobilized species while red cells, white cells and platelets are retained within the annulus 16. For direct control of the device output, an external pump can control the rate of plasma separation and contact time with the immobilized species thereby affecting the overall conversion. Plasma flow rate is directly related to the rotation rate of the inner cylinder 14 which creates the necessary shear rates to avoid membrane clogging and the physical properties of the membrane.

The apparatus 10 of Figures 1 and 2 can be employed to sufficiently remove drugs or toxins from whole blood if the appropriate immobilized species is used. An example is immobilized heparinase or urease for the removal of heparin or urea,

respectively. Other immobilized species may bind to or break down materials such as β_2M and various drugs which may be subject to overdose (*e.g.*, tricyclic antidepressants).

An immobilized heparinase will have a great impact in the treatment of acute renal insufficiency. Fig. 5 shows a patient 66 connected in a dialysis circuit. Blood from the patient 66 travels through a line 68 and is infused with heparin at 70. The heparinized blood is then pumped through dialyzer 72. The heparinized blood then travels into the vortex flow plasmapheretic reactor 10 of the invention.

The device 10 removes heparin by breaking it down and blood is then returned to the patient through the line 74. Anticoagulation is one of the most important components of renal replacement therapy and heparin is the oldest and most frequently used anticoagulant. In patients suffering from acute renal failure, the risk of bleeding is greatly increased and excessive anticoagulation may be the source of bleeding complications reported to occur in 5-26% of treatments. Current alternatives to systemic heparinization include variable heparin dosing, low molecular weight heparin, regional heparinization and neutralization with protamine, regional citrate anticoagulation with trisodium citrate, nefamostat mesilate, and prostaglandin analogue infusion. Despite these alternatives, acute kidney failure is a serious problem with unmet need for effective deheparinization.

The immobilized heparinase reactor of the invention is used in a regional heparinization regime and either of the two currently accepted methods to treat acute kidney failure: continuous renal replacement therapy (CRRT) and intermittent hemodialysis (IHD). In regional heparinization, heparin is infused into the circuit proximal to the dialyzer and the heparinase reactor located distal to the dialyzer degrades most of the heparin. With this configuration the patient has minimal exposure to heparin. The heparin degradation fragments have a much lower anticoagulant activity.

Preliminary in vitro tests of the reactor 10 of the invention with human blood have shown significant deheparinization and negligible blood damage. In addition, many experiments have been performed on live sheep. Results of these experiments are presented below in the Examples.

It is thus seen that the vortex flow plasmapheretic reactor of the invention efficiently removes drugs or toxins from whole blood when the appropriate immobilized species is used. The apparatus allows efficient and safe simultaneous separation and reaction within a compact device capable of handling whole blood. An important aspect of the invention is the circumparential flow in the active compartment via periodic membrane undulations. It is also important that there is no contact between blood cells and the immobilized species which will allow the use of the present apparatus in systems that employ proteins or enzymes that could damage the cell membrane such as phospholipase A_2. The system is compatible with whole blood which eliminates the need for separate external plasma separators which would involve extra costs and monitoring. Importantly, there is no net concentration of cells within the device and the device has the capability to lower the hematocrit of the blood only within the device to improve plasma flux through the membrane. The apparatus does not damage blood cells (hemolysis platelet aggregation), and there are no blood flow limitations. There is low priming volume (80 ml or lower), and the apparatus is easy to use in a clinical setting.

The apparatus of the invention can also be effectively used to remove toxins from blood without the use of an immobilized species via plasmapheresis as discussed above in conjunction with Fig. 3. In this embodiment, superior plasma fluxes (e.g. 50 ml/min) and longer operation times (up to 5 continuous hours without clogging) result from the design of the invention. This plasmapheresis technique is lower cost relative to the use of current systems which employ expensive hollow fiber filters or complicated and costly centrifugal devices. This aspect of the invention results in a significant improvement to the donation of plasma using the Baxter Autopherisis C unit due to the elimination of concentrated cell reinfusion cycles. This aspect cuts the donation time in half, lowers the anticoagulant dose needed to keep the system from clotting, and maintains a continuous process which allows for improved safety for the donor. The physical characteristics and fluid dynamics of the novel bioreactor design of the invention also have application in the research laboratory as an aid to carry out selective adsorption reaction processes with simultaneous separation of components. The mixing in the compartments helps minimize the processing time.

The bioreactor design of the invention is also applicable to nonbiological applications. For example, a series of compartments may be separated by membranes of successively reduced pore size as described above in conjunction with Fig. 4. Such a reactor can be used for efficient continuous size separation of solid particles in a slurry. As described above, the undulations of the membrane help keep the particles of the slurry fluidized, allowing the smallest particles to quickly pass through the membranes of successively reduced pore size to the final compartment. In another example, the reactor design may be used for catalysis of one or more components of mixtures or slurries. For example, a liquid phase may be separated from a solid phase as described above, and catalysts or reactants may be bound to solid supports for treatment of the liquid phase. This may be desirable, for example, in systems where the solid phase tends to poison the catalyst. Examples of suitable catalysis systems may be found in a number of chemistry texts, such as Crabtree, *The Organometallic Chemistry of the Transition Metals*, Wiley & Sons, 1988, particularly at Chapter 9.

Examples

Materials, assays, and methods

The equipment and methods used in the following examples were as follows: The reactor vessel was made from concentric polycarbonate cylinders (6.38 cm OD and 5.10 cm OD with 0.32 cm wall thickness) and sheets with polycarbonate inlet and outlet ports (0.357 cm ID). The gap between the inner cylinder and the membrane was 0.17 cm. The priming volume of the reactor was 45 ml, and the total reactor volume was 70 ml. The inner cylinder had a radius of 2.70 cm, and rotated on 0.32 cm OD stainless steel pins. Microporous polyester membranes (1 μm pore size) covered 11 cm of the 15 cm reactor length. Silicone O-rings were used to seal the inlet and outlet ports. Rotation of the inner cylinder was achieved via magnetic coupling of eight neodymium iron boron disc magnets (Dia = 1.28 cm, Length = 0.64 cm) and an external electric motor and controller. Rotation rate was detected through an optical sensor and displayed on a digital panel meter. Temperature measurements were made by T-type thermocouples connected to a digital panel meter.

Medical grade heparin for blood studies was porcine, 1,000 units/ml. Powdered heparin for enzyme activity determination was also porcine, 166 units/mg.

Normal saline (0.9% NaCl) and PBS (0. 154 M NaCl and 0.01 M sodium phosphate, pH = 7.4) were used. Heparin levels in blood were monitored with Hemochron coagulation timers and glass activated test tubes.

Agarose particles were 6%, 100-200 mesh, 100 μm average diameter. Heparinase was produced from *Flavobacterium heparinum*. The enzyme preparation was 95% pure heparinase as determined by RP-HPLC (Company Documentation) with a specific activity of 242 IU/ml and a protein concentration of 2.6 mg/ml. One IU (international unit) is defined as the amount of enzyme required to produce 1 μmol of product per minute. Human blood was obtained from healthy male and female volunteers. Plasma hemoglobin levels were determined with an assay kit from Sigma Chemical Company (St. Louis, MO).

An assay using Azure 11 dye was used to monitor heparin concentrations during the experiments, according to the technique of Lam, "The separation of active and inactive forms of heparin," *Biochem. Biophys. Res. Commun.* **69**:570-577, 1976, which is incorporated by reference herein. A 4.5 ml volume of the Azure II dye solution (0. 0 1 mg/ml) was added to 0.5 ml of the heparin solution to be tested. The sample was mixed and incubated at room temperature for 1 minute before measuring the absorbance at 500 nm. A standard curve for this assay was prepared by using solutions of known heparin concentrations ranging from 0 to 3 USP units/ml heparin (~ 0 - 19 μg/ml). The standard curve was linear in the above range.

Whole blood recalcification times (WBRT) were used to indirectly determine the amount of heparin present in blood. Initially, a 200 μl volume of citrated blood (3.8% 1:10 dilution) was added to Hemochron ACT test tubes containing glass particles. Next, 200 μl of $CaCl_2$ was added to the test tube and the Hemochron 801 clot timer machine was immediately started. The test tube was gently mixed for 10 seconds and inserted into the test well of the Hemochron 801. The time required for a clot to form was recorded. The unknown samples were compared to a standard curve which was linear in the range of 0 - 4 USP units heparin/ml blood.

The Coomasie blue dye method of Bradford was used to measure the concentration of heparinase in buffered saline. A 800 μl sample was mixed with 200 μl of dye solution and incubated at room temperature for 5 minutes. The absorbance at 595 nm was measured and compared to a standard curve prepared with known

bovine serum albumin concentrations ranging from 0 to 15 μg/ml. The standard curve was linear in this range.

The activity of heparinase I was defined using the international unit (IU). One IU is defined as the amount of heparinase that would produce 1 μmol of double bonds/min. The appearance of heparin degradation products was monitored at 232 nm in a quartz cuvette. Briefly, 20 gl of heparinase solution was added to 3 ml of heparin solution (2 mg/ml, in 100 mM MOPS and 5 mM calcium acetate pH 7.4) at 30°C. The initial rate was calculated from the slope of the curve and converted to IU using 3800 M^{-1} molar absorptivity (1 cm path length).

One volume of agarose gel (100 μm average bead diameter) was washed with 10 volumes of deionized (DI) water to remove any preservatives. After resuspending the gel in 1 volume of DI water and 2 volumes of 2 M sodium carbonate, the suspension was chilled in an ice bath. Next, 0.15 volume of a cyanogen bromide in acetonitrile (1 g/ml) solution was added to the gel mixture, after which it was stirred vigorously in the fume hood for 5 minutes. Using a sintered glass funnel, the activated gel was isolated and washed with a mixture comprising 50 volume % DI water, 25 volume % I mM hydrochloric acid, and 25 volume % 0.1 M sodium bicarbonate 0.5 M NaCl pH 8.3 buffer.

After extensive washing of the activated gel, the heparinase solution (18 mg in 100 ml 0.1 M sodium bicarbonate 0.5 M NaCl pH 8.3) was incubated with the beads (100 ml) at 4°C for 5 hrs to allow binding. Following heparinase binding, the immobilized heparinase was incubated overnight at 4°C in a lysine solution (0.2 M lysine hydrochloride, 0.1 M sodium bicarbonate, and 0.5 M NaCl) to cap any unreacted sites. The immobilized heparinase was washed with a solution comprising 11 volume % cold pH 8.3 buffer and 67 volume % phosphate buffered saline (pH 7.4), and 22 volume % distilled water. The amount of bound protein was determined by a mass balance between the original enzyme solution and the washes.

The activity of the heparinase bound to the beads was measured using a modified UV 232 activity assay. A known volume of beads, approximately 0.1 ml, was added to 4 ml of a heparin solution (25 mg/ml). Under vigorous swirling at 37°C, 0.1 ml samples were taken at 1 minute intervals for 4 minutes and quenched in 0.9 ml of 30 mM HCl. The samples were centrifuged and the absorbance of the

supernatant was measured at 232 nm. The activity was calculated from the slope between the data points using 5000 M^{-1} as the molar absorptivity.

For the β_2M studies, eleven murine, anti-β_2M hybridoma cell lines have been produced following standard techniques, as summarized in Schlebusch, *et al.*, "Production of a Single-Chain Fragment of the Murine Anti-Idiotypic Antibody ACA125 as Phage-Displayed and Soluble Antibody by Recombinant Phage Antibody Technique," *Hybridoma* **16**(1):47-52, 1997, incorporated herein by reference. DNA polymerase chain reaction (PCR) was used to amplify the variable heavy (V_H) and variable light (V_L) sequences from hybridoma-derived complementary DNA. Through their ligation to a DNA strand encoding a polypeptide "linker," these V_H and V_L sequences were used to make single-chain antibody fragment (scFv) sequences, which were subsequently inserted into a plasmid vector. One scFv plasmid has been successfully expressed in *E. coli.* and qualitatively shown to bind β_2M (Western blot). It will be apparent to those skilled in the art that these techniques can be used to generate a variety of scFvs specific for β_2M. Should it be found that the β_2M in amyloid deposits is antigenically distinct from recombinant β_2M (for example, due to end-stage glycation), antibodies may be produced using β_2M obtained directly from clinical material (amyloid deposits). It is expected that 1-10 mg of such material will suffice to generate a second generation of monoclonal antibodies for scFv generation.

Example 1 - Deheparinization in saline

Regional heparinization studies were performed with the vortex flow plasmapheresis reactor (VFPR) of the invention. A 500 ml volume of the feed solution, heated to 32°C, was recirculated through the circuit at 120 ml/min with the plasma pump adjusted to 60 ml/min. The feed solution consisted of 100 mM MOPS and 5 mM $CaCl_2$ in isotonic saline adjusted to pH 7.4. The rotation rate of the inner cylinder was set to 1,200 rpm, which corresponds to a shear rate of 9,200 s^{-1}. This shear rate is below the hemolysis limit of 20,000 s^{-1} reported in the literature (Heuser, *et al.*, "A couette viscometer for short time shearing of blood," *Rheology*, **17**:17-24, 1980; Fischel, *et al.*, "Couette membrane filtration with constant shear stress," *Trans. Am. Soc. Artif. Intern. Organs*, **34**:375-385, 1988). Approximately 20 ml of immobilized heparinase (Specific activity 10-15 IU/ml wet gel) was injected into the

active volume compartment of the VFPR and was fluidized by the flow dynamics in that chamber. The priming volume of the chamber was 45 ml. The infusion of heparin prereactor was adjusted to achieve clinically relevant heparin plasma concentrations which are in the range of 5 - 12 μg heparin/ml plasma. Heparin concentrations were measured at the inlet and outlet of the reactor using the Azure II assay.

As discussed earlier, the VFPR design was intended to overcome the "blood compatibility" and throughput issues associated with agarose immobilized heparinase I. The results of the VFPR experiments in saline are shown in Fig. 6. The reactor maintained mean inlet and outlet heparin concentrations of 11 ± 0.5 and 6.0 ± 0.2 μg/ml (± S.E.M.), respectively. These values corresponded to a mean heparin conversion of 44 ± 0.5% (± S.E.M.) for an inlet flow rate into the reactor of 120 ml/min and a plasma pump flow rate of 60 ml/min. This heparin conversion, if achieved in a patient, would meet the minimum efficacy design criteria for an immobilized heparinase reactor as stated in the Introduction. It is expected that the overall heparin conversion through the device would depend on the amount of immobilized enzyme, the fluidization conditions, and the flow split through the microporous membrane.

Example 2 - Deheparinization in sheep

The bioreactor configuration of Fig. 1 was tested in live sheep, and the results are presented in Figs. 7-17. In Fig. 7 heparin concentrations at the reactor inlet are shown by the circles and at the outlet by squares. The flow rate was 120 milliliters per minute which is equivalent to 200 milliliters per minute whole blood assuming a hematocrit of 40. The temperature of the experiment was 33 °C. Fig. 8 shows reactor conversion in saline and a flow rate of 120 milliliters per minute (200 milliliters per minute whole blood assuming a hematocrit of 40). The temperature of this experiment was 33 °C. Fig. 9 shows inlet and outlet whole blood recalcification times for the immobilized heparinase reactor. Blood flow rate was 150 millimeter per minute and base line WBRT was 115 seconds. Reactor temperature was 36 °C. Fig. 10 shows conversion for immobilized heparinase reactor at a blood flow rate of 150 milliliter per minute. The theoretical target conversion was 40%. Fig. 11 shows

reactor blood compatibility data for sheep. Fig. 12 illustrates total protein during extracorporeal procedure with immobilized heparinase reactor. Fig. 13 shows inlet and outlet heparin levels for immobilized heparinase reactor in another sheep experiment. Blood flow rate was 150 milliliters per minute and base line WBRT was 115 seconds. Fig. 14 illustrates reactor blood compatibility data for sheep. Fig. 15 is a graph showing total protein during the extra corporeal procedure with immobilized heparinase reactor. Fig. 16 shows reactor conversion with time. Blood flow rate was 150 milliliters per minute.

Fig. 17 shows heparin effect as a function of time. The base line whole blood recalcification time (WBRT) of the donor was 112 seconds. The circuit was heparinized to an initial WBRT of 341 seconds and the reactor reduced it to a final WBRT of 140 seconds. For deheparinizations number 2 and number 3, the circuit was reheparinized from 140 seconds to 340 and 350 seconds, respectively. The final WBRT for deheparinization number 2 and number 3 were 140 and 150 seconds, respectively. The data are an average of four measurements on a Hemochron 801 clotting time tester (International Technidyne Corporation).

Example 3 - Deheparinization of human whole blood

The assembled reactor was incorporated into a closed circuit primed with normal saline. The circuit consisted of a blood warmer, blood pump, drip chamber and pressure monitor. The experimental set up was similar to the VFPR saline studies. A 450 cc volume of human donor blood was collected in heparin at the Blood Donor Center of Children's Hospital of Boston. The hematocrit (% of blood cells) of the bag was adjusted to 30-35 % by dilution with saline to match the values normally encountered in the clinical setting. The blood was pumped at a flow rate of 160 ml/min. The VFPR rotation rate was set at 1,200 rpm and the plasma pump was set at 60 ml/min. The temperature of the blood circuit was constant at 33°C. A pressure gauge was placed between the active volume compartment outlet and the plasma pump to monitor clogging of the microporous membrane. Blood samples were taken at the inlet and outlet of the device and heparin levels were indirectly assayed by WBRT's. Blood samples also were drawn at the reactor outlet for further hemocompatibility tests.

Even though good heparin neutralization results were obtained in the saline experiments of Example 1 and the sheep experiments of Example 2, the important measure for an immobilized heparinase reactor is its performance in human blood. The results for regional blood heparinization using 10 ml of agarose immobilized heparinase (specific activity 16 IU/ml gel) are shown in Fig. 18. The reactor maintained a mean WBRT difference of 67 seconds between the inlet and outlet. This difference corresponded to a mean heparin conversion of 34 ± 2% (± S.E.M.) at a blood flow rate of 160 ml/min and a plasma pump flow rate of 60 ml/min.

Blood was tested before and after the deheparinization experiment to determine whether the treatment caused any blood damage. It was found that white and red cell counts changed by less than 3% of their initial values. The platelet count had an 8% reduction relative to the concentrations at the beginning of the run. The concentrations of free hemoglobin released into the plasma were well below the safety criteria of 150 mg/dL. Therefore, eliminating contact between the cells and the agarose beads was an efficient way to significantly reduce hemolysis. These results are favorable when compared to those of previous immobilized heparinase reactors in which fluidized agarose beads within whole blood negatively affected the cell counts (*e.g.*, Larsen, *et al.*, "Effect of extracorporeal enzymatic deheparinization on formed blood components," *Artif. Organs*, 8(2):198-203, 1984).

It is important to know whether an extracorporeal device is nonspecifically depleting proteins in blood. This is especially important for an immobilized heparinase reactor because the anticoagulant activity of heparin in blood depends on the presence of many other proteins in the "clotting cascade", specifically antithrombin III. Relative changes in total serum protein, antithrombin III, and fibrinogen for a reactor run were measured to assess this aspect of reactor performance. Total protein (primarily albumin and immunoglobulins) and antithrombin values were unchanged during the experimental run. Fibrinogen, a precursor protein to fibrin clots and a measure of the degree of fibrin generation within the system, dropped 13% over the course of the 60 minute run. Nevertheless, there were no fibrin clots visible to the naked eye upon inspection of the device after the experimental run. This observation does not rule out the possibility that microclots may be forming on the surface of the beads. However, the VFPR was

considered to have fulfilled the safety design criteria regarding device effect on blood cells and platelet count.

Example 4 - Removal of β_2M from blood

A preliminary study of the removal of β_2M using the bioreactor of the invention has been carried out. The scFvs used in the study have several advantages, including reduced cost, smaller size (and therefore higher achievable density), and relatively easy surface immobilization.

The scFvs are bound with a polypeptide linker that can be engineered to bind to a variety of supports. For example, any primary amine (lysine side chain) can be biotinylated using the biotin derivative, biotin N hydroxysuccinimide ester. The biotinylated polypeptide or antibody can then be conjugated to any solid support with an accessible avidin or streptavidin molecule. For example, streptavidin coated agarose beads are commercially available (Promega, Madison, WI) and can be used as a solid support for the scFvs. As will be apparent to those skilled in the art, many other binding systems are possible and the exact characteristics of the linker and the binding system are not intended to limit the invention. As another specific example, the scFvs could be bound to liposomes by alkylation/esterification with fatty acid derivatives, as described in DeKruif, *et al.*, "Biosynthetically lipid-modified human scFv from phage libraries as targeting molecules for immunoliposomes," *FEBS Lett.* 399:232-236, 1996, incorporated herein by reference. It may be desirable to use hydrophilic supports in order to promote dispersion of the supports in the plasma.

The scFvs have the further advantage that site-directed or random mutagenesis can be used to further boost β_2M affinities by as much as one or two orders of magnitude, to a binding affinity on the order of 10^8 or more. See, for example, Schier, *et al.*, "Isolation of picomolar affinity anti-c-erbB-2 single chain Fv molecular evolution of the complementarity determining regions in the center of the antibody binding site," *J. Mol. Biol.* 17:551-567, 1996, incorporated herein by reference. The scFvs may, for example, be engineered to contain an unpared thiol close to or at the $COOH^-$ terminus of the scFv, by introduction of a cysteine residue. This mutation may facilitate binding of the scFv by a strepavidin-based approach, for example.

This study assessed the feasibility of immobilized antibodies to adsorb β_2M from solution and approximated the capacity of such a system. From the measured data an estimation of the reactor size required to clear 0.2 gm of β_2M was formulated. Commercially available, intact anti-β_2M antibodies (BBM.s; 150 k Da) were bound to Protein A beads in an oriented fashion, with the β_2M binding sites exposed. An average of 0.05 μM of BBM.1 bound per ml of beads. Studies were conducted in 1 ml columns, where it was found that in saline containing 60 μg/ml of β_2M about 0.04 μM of β_2M per ml of beads was removed in one hour, suggesting an approximate antibody-antigen binding ratio of 1:0.8. Extrapolating these data to scFv (27 k Da), and assuming the same binding ratio and affinity and a 40% bead volume in the reactor, 0.2 g of β_2M can be removed by a 350 ml active volume. In a typical dialysis session, the reactor should remove at least 0.2 g (the circulating concentration of β_2M) in order to halt β_2M accumulation, and possibly 0.5 g or more in order to restore elevated β_2M levels to normal.

This represents a maximum reactor volume, however. The VFPR described above has much higher mass transfer rates than a packed column, and it is therefore expected that much smaller active volumes can be achieved. Improvement of the binding affinity of the scFvs by mutagenesis as described above is expected to further reduce the necessary reactor volume, and it is believed that active volumes of 50 ml or less are readily achievable while meeting target β_2M removal levels.

Other embodiments of the invention will be apparent to those skilled in the art from a consideration of the specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. Apparatus for removing a substance from whole blood comprising:

concentric outer and inner cylinders defining an annulus therebetween, the inner cylinder adapted for rotation with respect to the outer cylinder;

at least one of an inner surface of the outer cylinder or an outer surface of the inner cylinder including a porous membrane covered portion forming a compartment containing an immobilized species, the species adapted to remove the substance;

an inlet for introducing blood into the annulus for flow along the cylinders; and

an outlet port for discharging the blood,

wherein the porous membrane allows plasma within the blood to interact with the immobilized species while restricting blood cells from interacting with the immobilized species.

2. The apparatus of claim 1 wherein the rotation of the inner cylinder generates Taylor vortices in the annulus, the vortices creating oscillating pressure gradients within the annulus, the pressure gradients causing periodic undulations in the porous membrane resulting in circumferential flow in the compartment containing the immobilized species.

3. The apparatus of claim 1 or 2 wherein both inner and outer cylinders have membrane covered portions containing immobilized species.

4. The apparatus of claim 1 or 2 wherein the inner surface of the outer cylinder includes a recess covered by a mesh to exclude the immobilized species, the recess acting as a collection chamber for plasma after interaction with the immobilized species.

5. The apparatus of claim 4 further including a pump for circulating plasma from the recess into the annulus.

6. The apparatus of claim 1 or 2 wherein the species is immobilized on agarose beads.

7. The apparatus of claim 6 wherein the substance is heparin and the immobilized species is heparinase.

8. The apparatus of claim 1 or 2 wherein the substance is β_2-microglobulin and the immobilized species comprises single chain antibody fragments.

9. The apparatus of claim 8 wherein the apparatus is adapted to remove at least 0.2 g β_2-microglobulin in a period of less than about three hours.

10. The apparatus of claim 8 wherein the apparatus is adapted to remove at least 0.5 g β_2-microglobulin in a period of less than about two hours.

11. The apparatus of claim 8 wherein the apparatus has an active volume of less than about 350 ml.

12. The apparatus of claim 8 wherein the apparatus has an active volume of less than about 200 ml.

13. The apparatus of claim 8 wherein the apparatus has an active volume of less than about 50 ml.

14. The apparatus of claim 1 or 2 wherein the apparatus has a transmembrane flow rate of greater than about 50 ml/min.

15. The apparatus of claim 1 or 2 wherein the apparatus has a transmembrane flow rate of greater than about 100 ml/min.

16. The apparatus of claim 1 or 2 wherein the apparatus has a transmembrane flow rate of greater than about 200 ml/min.

17. The apparatus of claim 2 wherein the immobilized species is immobilized on beads, and wherein the beads are fluidized by the circumferential flow in the compartment.

18. The apparatus of claim 17 wherein the beads comprise a material selected from the group consisting of agarose, cellulose, and protein A.

19. The apparatus of claim 1 or 2 wherein the active species is in the form of micelles.

20. The apparatus of claim 1 or 2 wherein the inner cylinder rotates via magnetic coupling to an external motor.

21. The apparatus of claim 12 wherein the inner cylinder rotates at approximately 1200 r.p.m.

22. The apparatus of claim 1 or 2 wherein the active species is selected from the group consisting of antibodies, antibody fragments, catalytic antibodies, enzymes, peptides, proteins, or living cells.

23. Apparatus for collecting platelets from blood comprising:

concentric outer and inner cylinders defining an annulus therebetween, the inner cylinder adapted for rotation with respect to the outer cylinder;

at least one of an inner surface of the outer cylinder or an outer surface of the inner cylinder including two parallel porous membranes defining a first compartment therebetween and a second compartment between the membranes and the surface, the membrane closest to the surface having a pore size adapted to restrict the passage of platelets and the membrane farthest from the surface having a pore size adapted to allow the passage of platelets but to restrict the passage of other blood components;

an inlet for introducing blood into the annulus for flow along the cylinders;

means for removing platelets from the first compartment; and

an outlet port for discharging the blood.

24. A method of removing a substance from whole blood, comprising:

continuously isolating plasma from other blood components into a separate compartment, the separate compartment containing an active immobilized species, the species adapted to remove the substance to clean the plasma; and

remixing the cleaned plasma and the other blood components,

wherein continuously isolating comprises subjecting the blood to Taylor vortex flow.

25. The method of claim 24, wherein continuously isolating plasma includes passing the plasma through a filtration membrane having a pore size adapted to pass plasma but to restrict the passage of other blood components.

26. The method of claim 25, wherein continuously isolating plasma includes passing blood through an annular compartment defined by concentric inner and outer cylinders, the cylinders adapted for rotation with respect to one another, wherein the filtration membrane is disposed on at least one of an outer surface of the inner cylinder and an inner surface of the outer cylinder.

27. The method of claim 26, wherein the filtration membrane is flexible and undulates in response to the Taylor vortex flow.

28. The method of claim 24 or 27, further comprising collecting the substance removed from the plasma.

29. The method of claim 28, wherein the blood is from a transgenic animal engineered to secrete a desired compound in its blood, and wherein the substance removed is the desired compound.

30. The method of claim 24, wherein the substance is heparin or β_2-microglobulin.

31. A method of removing β_2-microglobulin from blood, comprising:

passing blood through a bioreactor, thereby continuously separating plasma from other blood components, exposing the separated plasma to an immobilized active species capable of binding to β_2-microglobulin, and remixing the exposed plasma with the other blood components,

wherein the bioreactor has a priming volume of less than about 500 ml and and a blood flow rate of greater than about 60 ml/min.

32. The method of claim 31, wherein the bioreactor comprises:

concentric outer and inner cylinders defining an annulus therebetween, the inner cylinder adapted for rotation with respect to the outer cylinder;

at least one of an inner surface of the outer cylinder or an outer surface of the inner cylinder including a porous membrane covered portion forming a compartment containing the immobilized active species;

an inlet for introducing blood into the annulus for flow along the cylinders; and

an outlet port for discharging the blood,

wherein the porous membrane allows plasma within the blood to interact with the immobilized active species while restricting blood cells from interacting with the immobilized active species.

33. The method of claim 32, wherein the rotation of the inner cylinder generates Taylor vortices in the annulus, the vortices creating oscillating pressure gradients within the annulus, the pressure gradients causing periodic undulations in the porous membrane resulting in circumferential flow in the compartment containing the immobilized species.

34. The method of claim 33, wherein the active species comprises single chain antibody fragments which bind to β_2-microglobulin.

35. A method for continuous treatment of a mixture comprising liquid and solid components, comprising:

concentric outer and inner cylinders defining an annulus therebetween, the inner cylinder adapted for rotation with respect to the outer cylinder;

at least one of an inner surface of the outer cylinder or an outer surface of the inner cylinder including a porous membrane covered portion forming a compartment containing a reactant for treatment of the liquid component of the mixture;

an inlet for introducing the mixture into the annulus for flow along the cylinders; and

an outlet port for discharging the mixture,

wherein the porous membrane allows the liquid portion of the mixture to interact with the reactant while restricting the solid portion of the mixture from interacting with the reactant.

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FIG. 1a

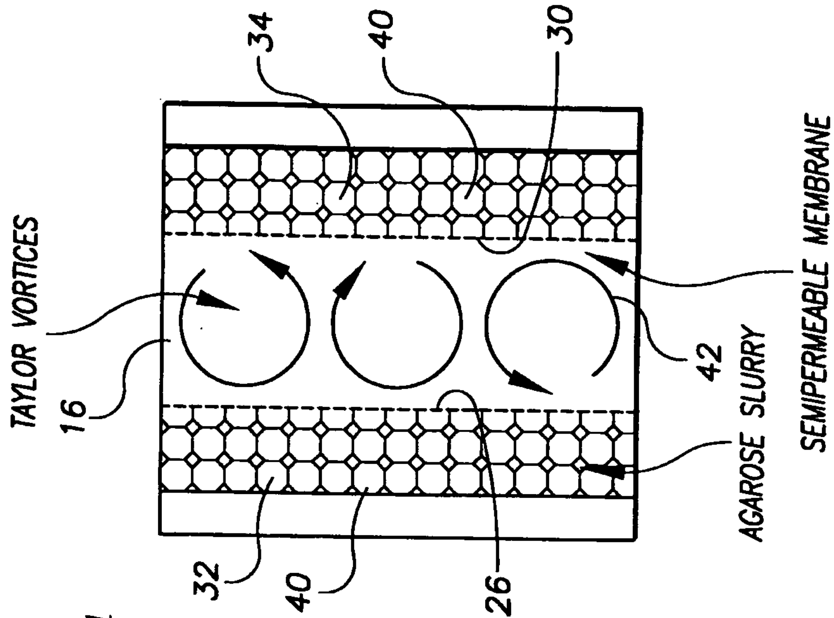
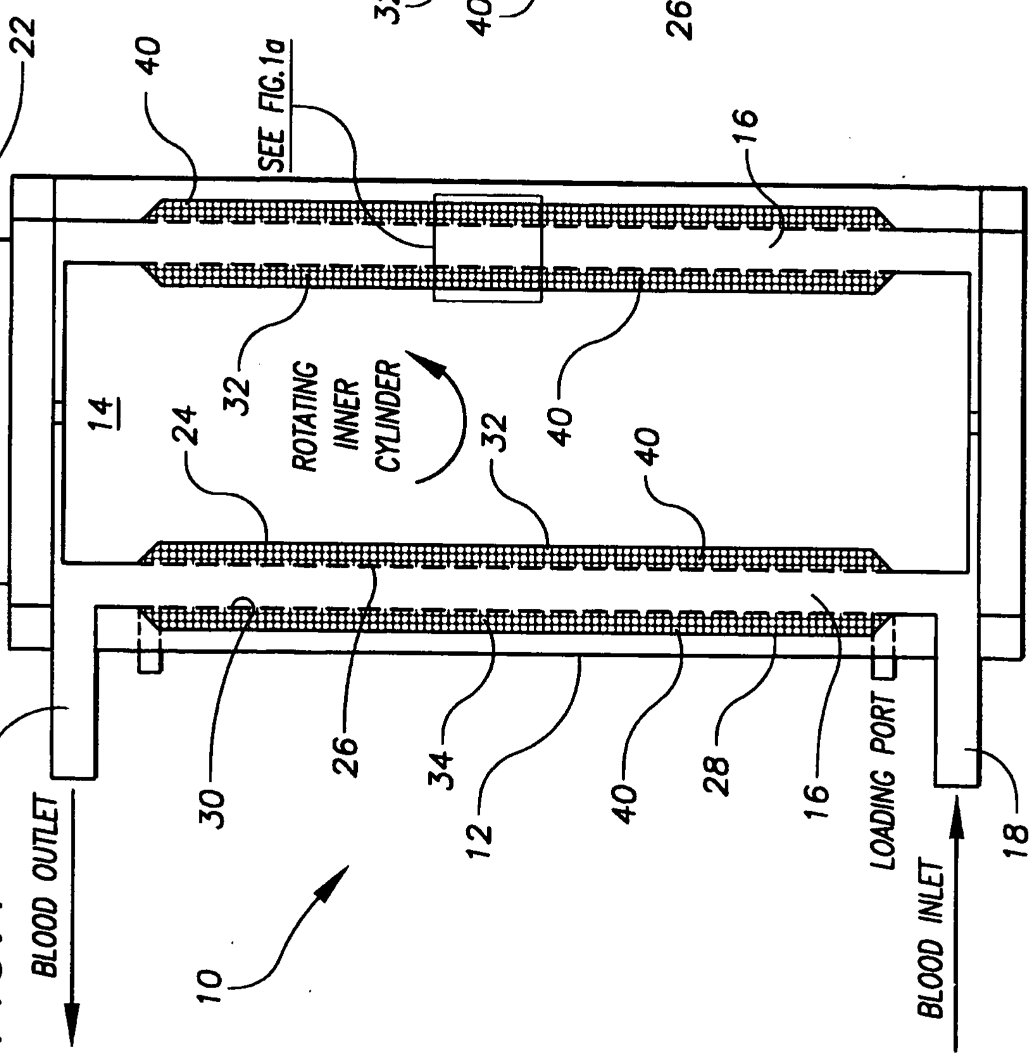


FIG. 1



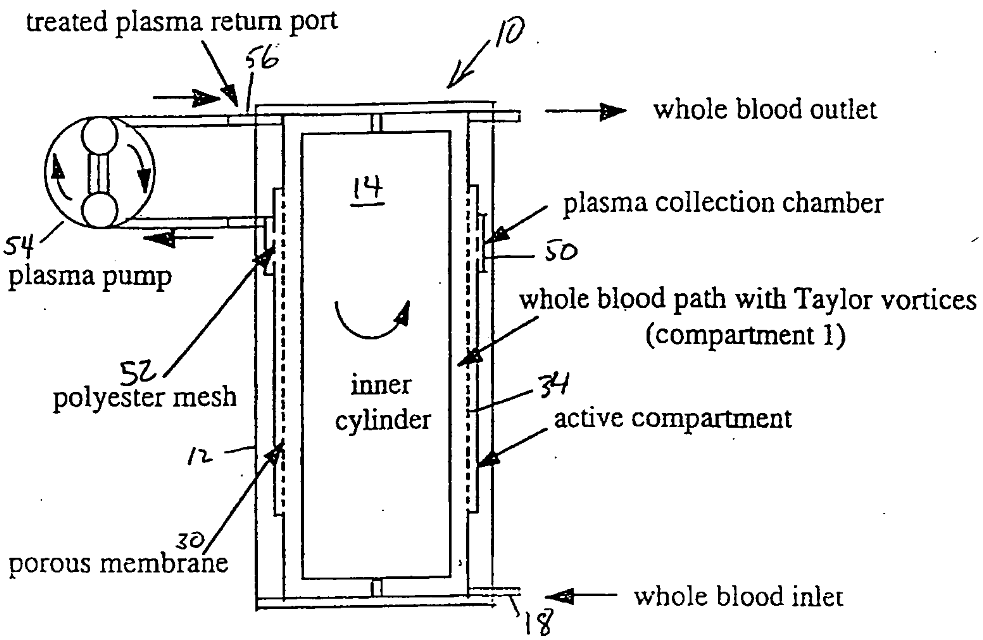

treated plasma return port
56
10
whole blood outlet
14
plasma collection chamber
50
54
plasma pump
whole blood path with Taylor vortices
(compartment 1)
52
polyester mesh
inner
cylinder
34
active compartment
12
30
porous membrane
whole blood inlet
18

FIG. 2

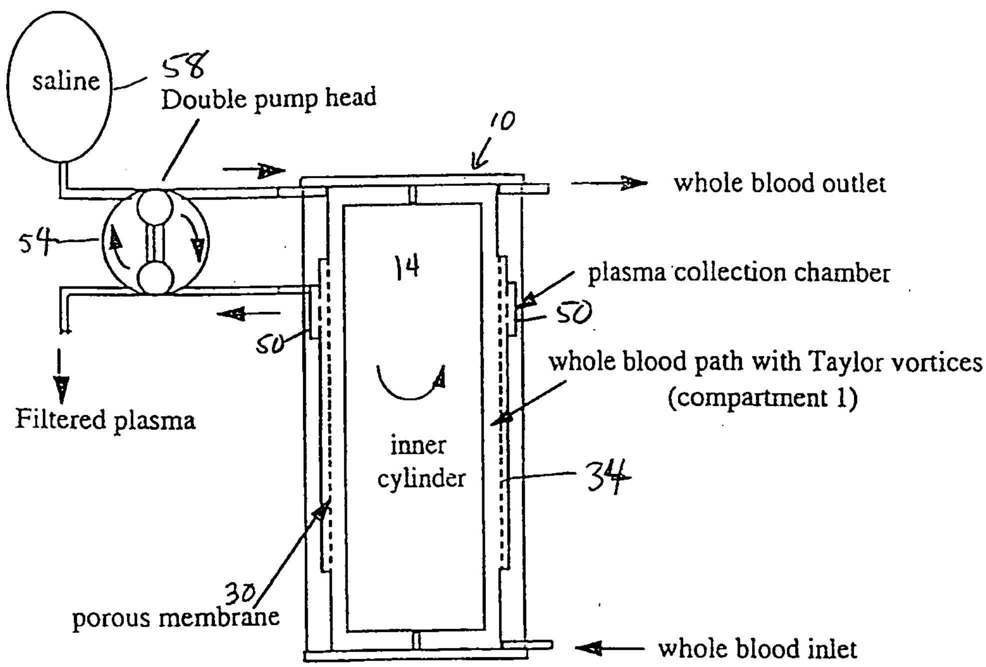
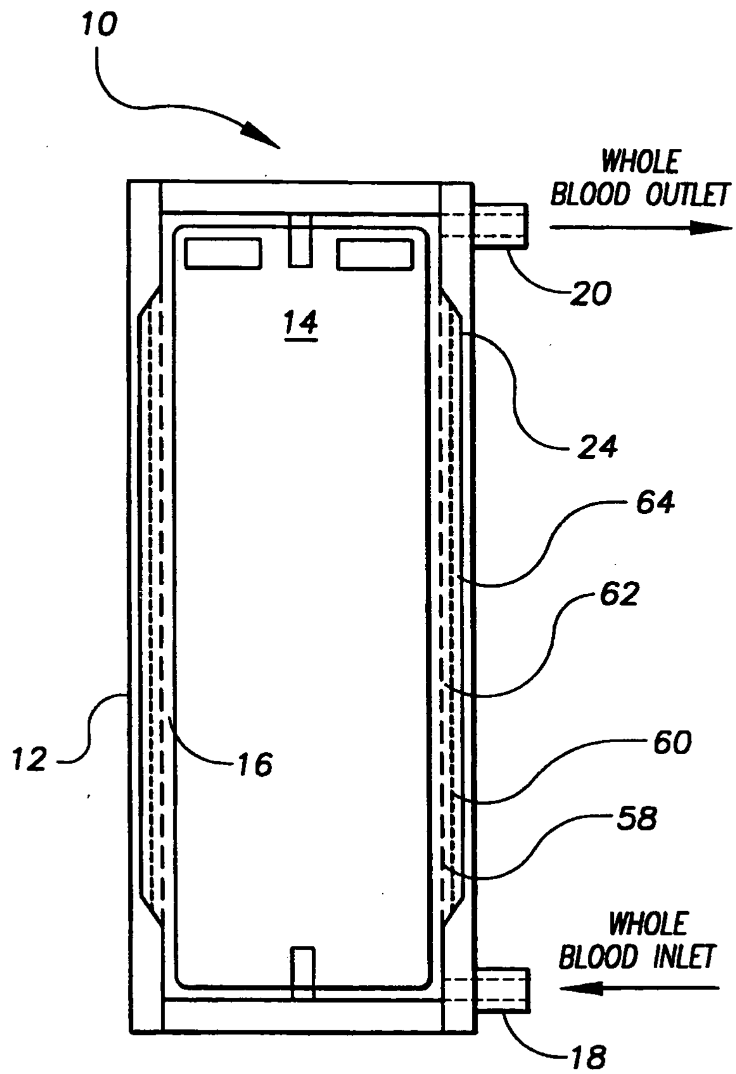

saline
58
Double pump head
10
whole blood outlet
54
14
plasma collection chamber
50
50
Filtered plasma
whole blood path with Taylor vortices
(compartment 1)
inner
cylinder
34
30
porous membrane
whole blood inlet

FIG. 3

FIG. 4


10
WHOLE BLOOD OUTLET
20
14
24
64
62
60
58
12
16
WHOLE BLOOD INLET
18

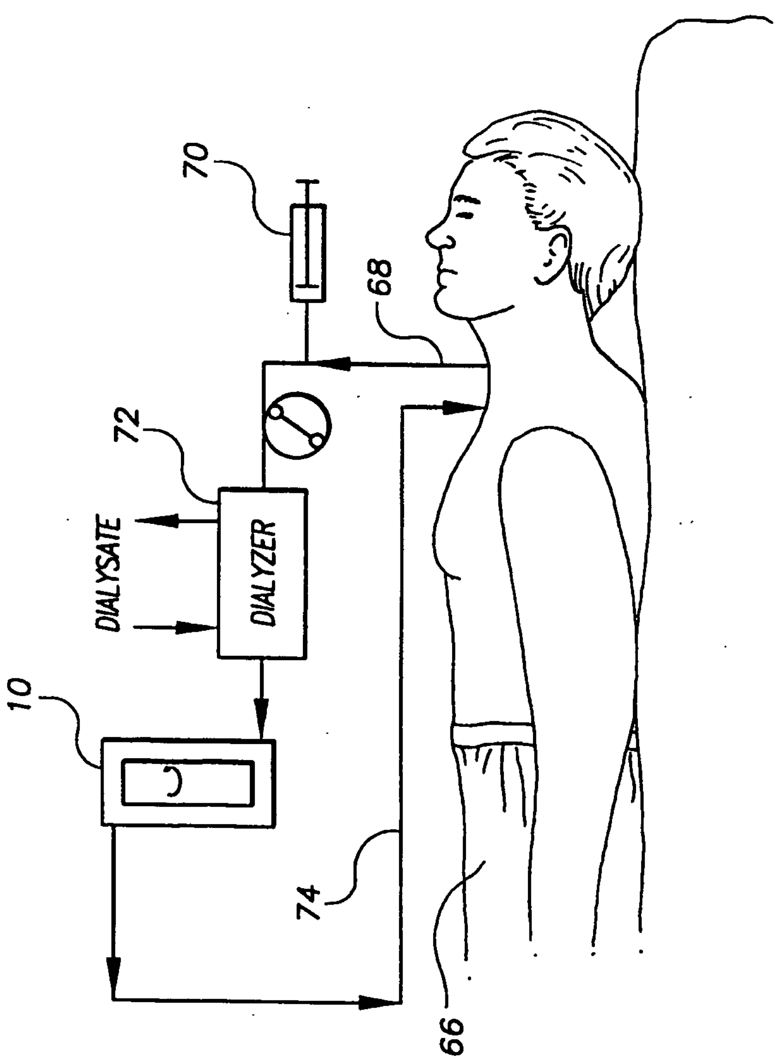


FIG.5

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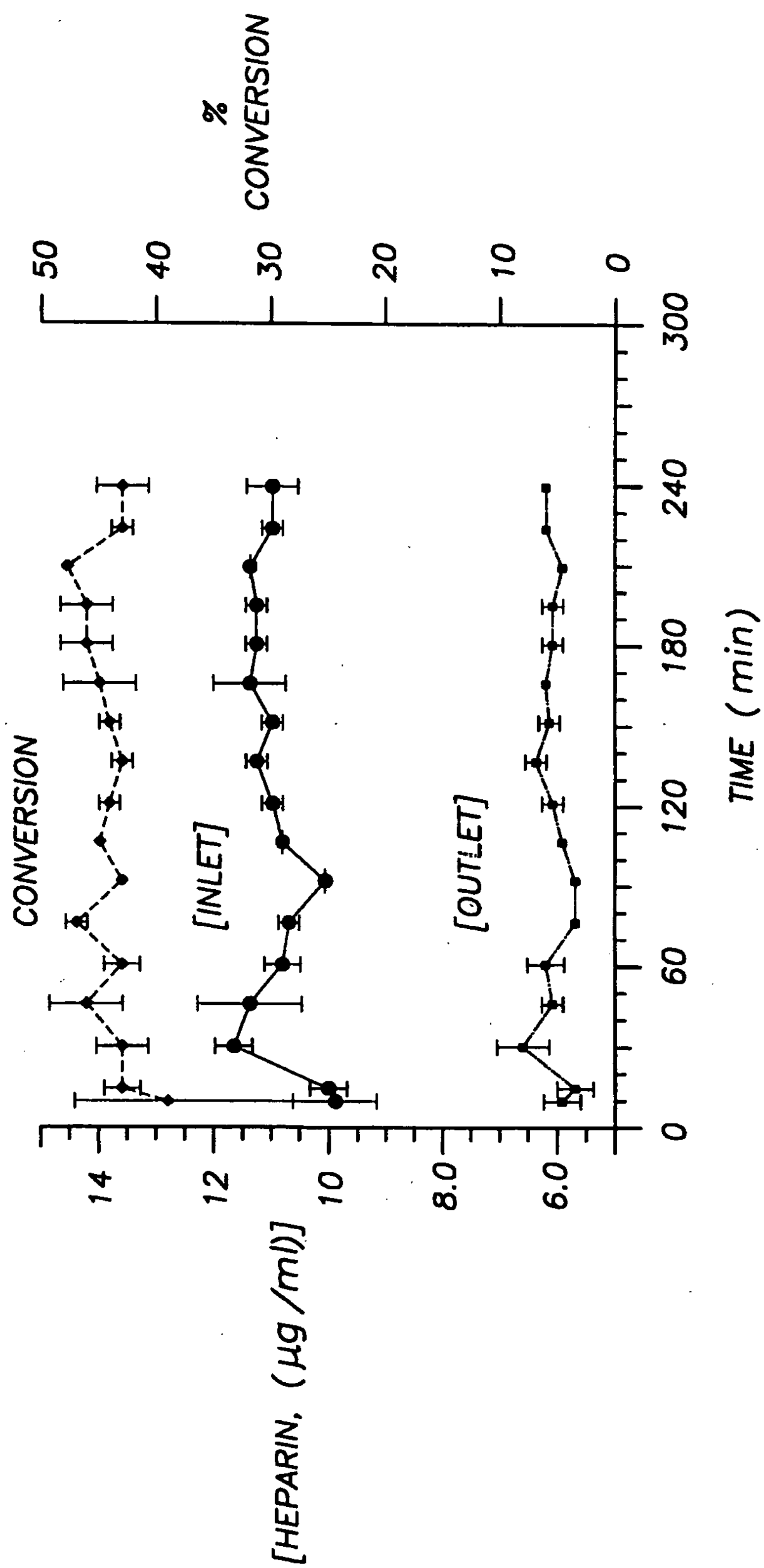
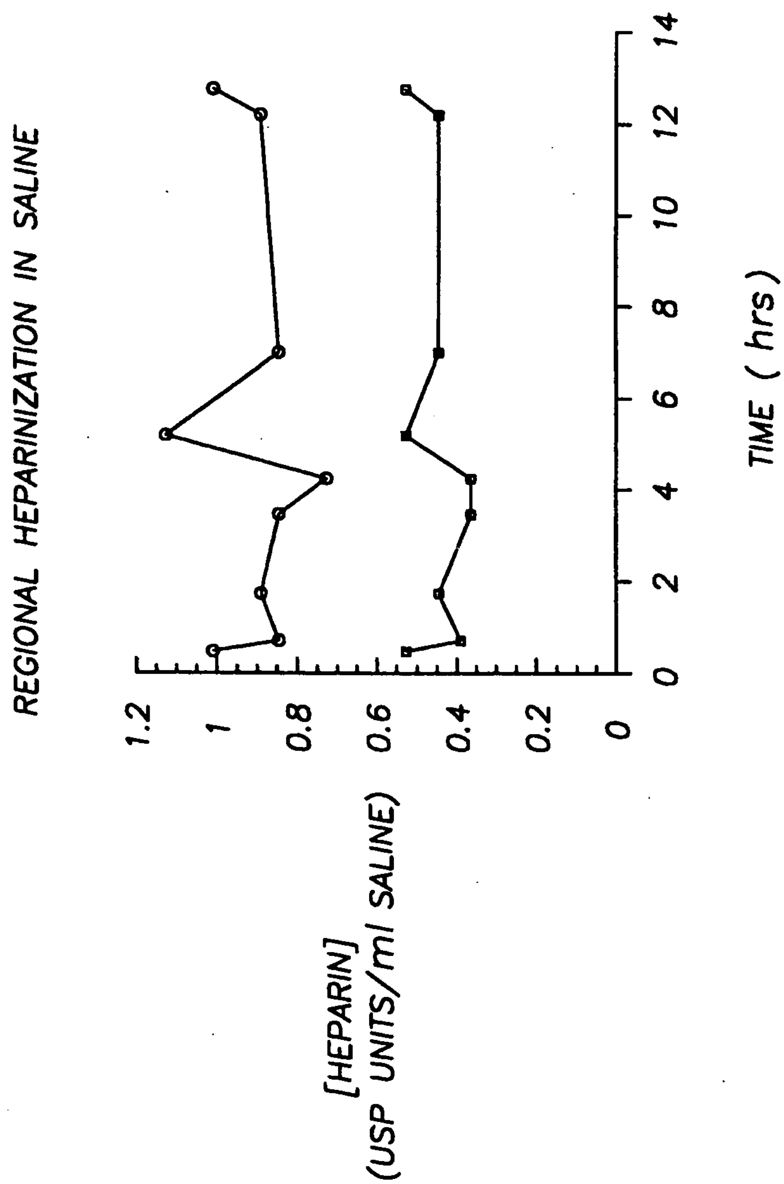
FIG.6



% CONVERSION
50
40
30
20
10
0
CONVERSION
[INLET]
[OUTLET]
14
12
10
8.0
6.0
[HEPARIN, (µg/ml)]
0
60
120
180
240
300
TIME (min)

FIG. 7


REGIONAL HEPARINIZATION IN SALINE
[HEPARIN]
(USP UNITS/ml SALINE)
1.2
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
12
14
TIME (hrs)

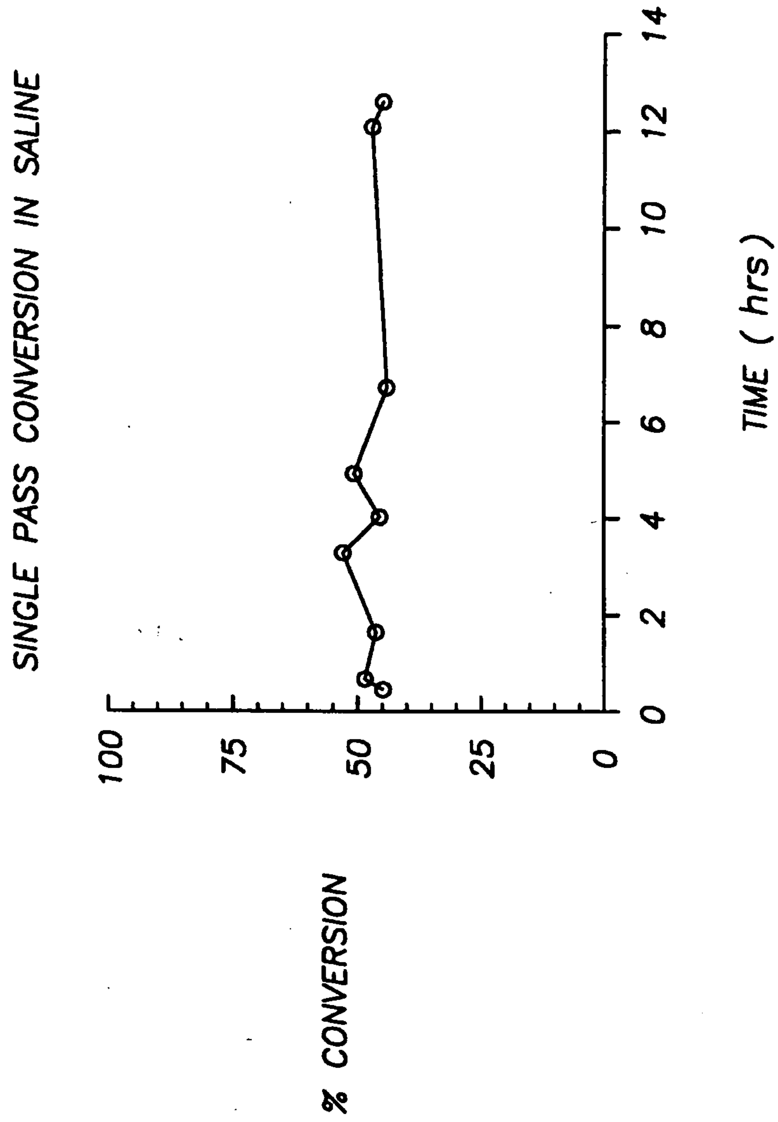
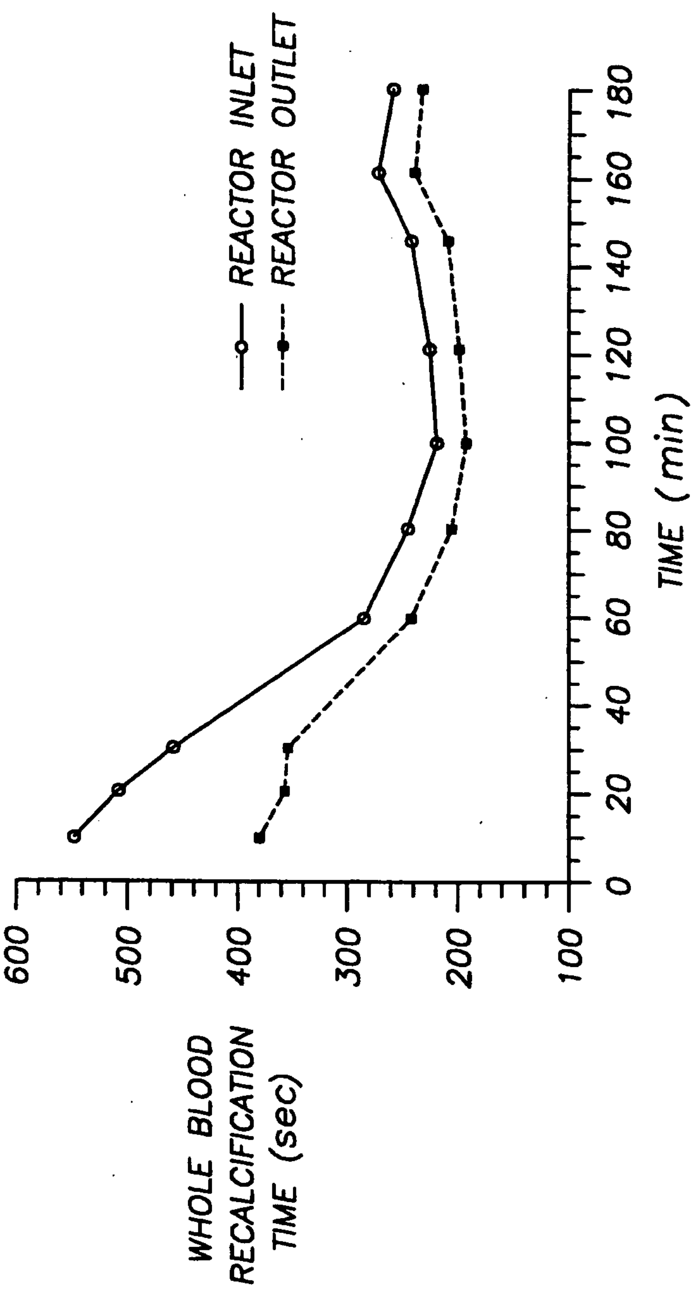

SINGLE PASS CONVERSION IN SALINE
% CONVERSION
100
75
50
25
0
0
2
4
6
8
10
12
14
TIME (hrs)

FIG.8

FIG.9


WHOLE BLOOD RECALCIFICATION TIME (sec)
600
500
400
300
200
100
0
20
40
60
80
100
120
140
160
180
TIME (min)
REACTOR INLET
REACTOR OUTLET

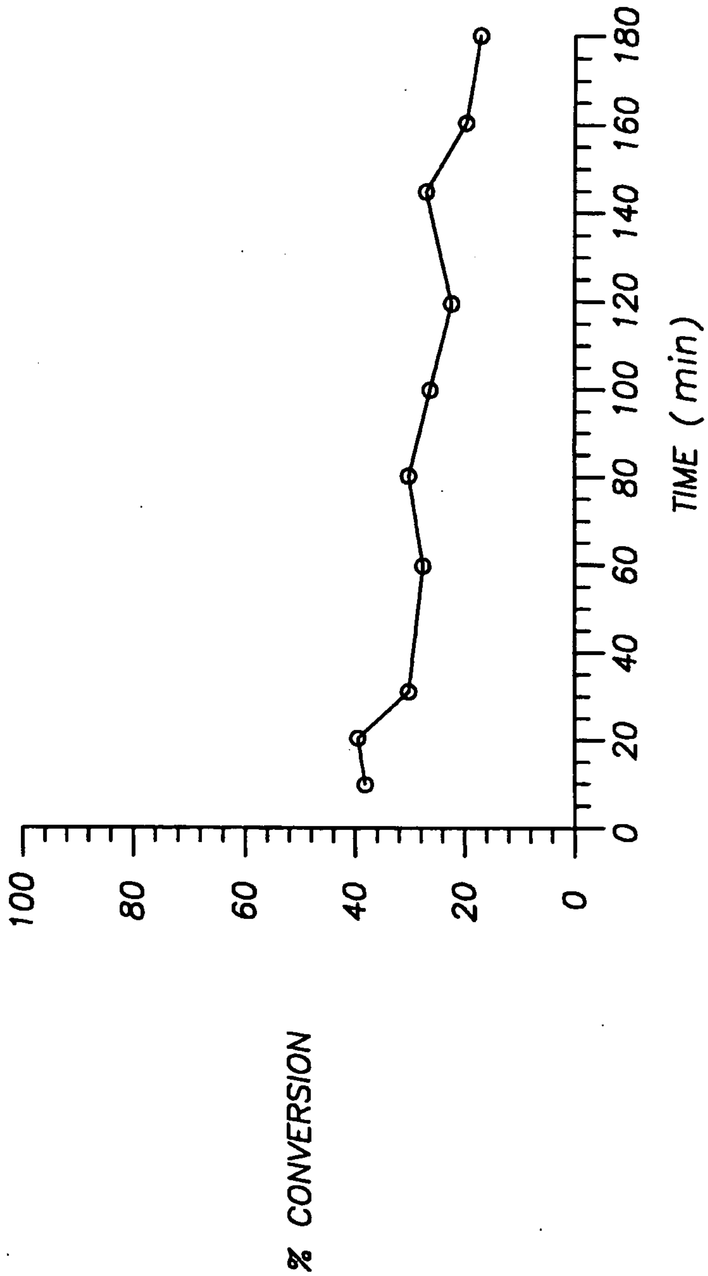
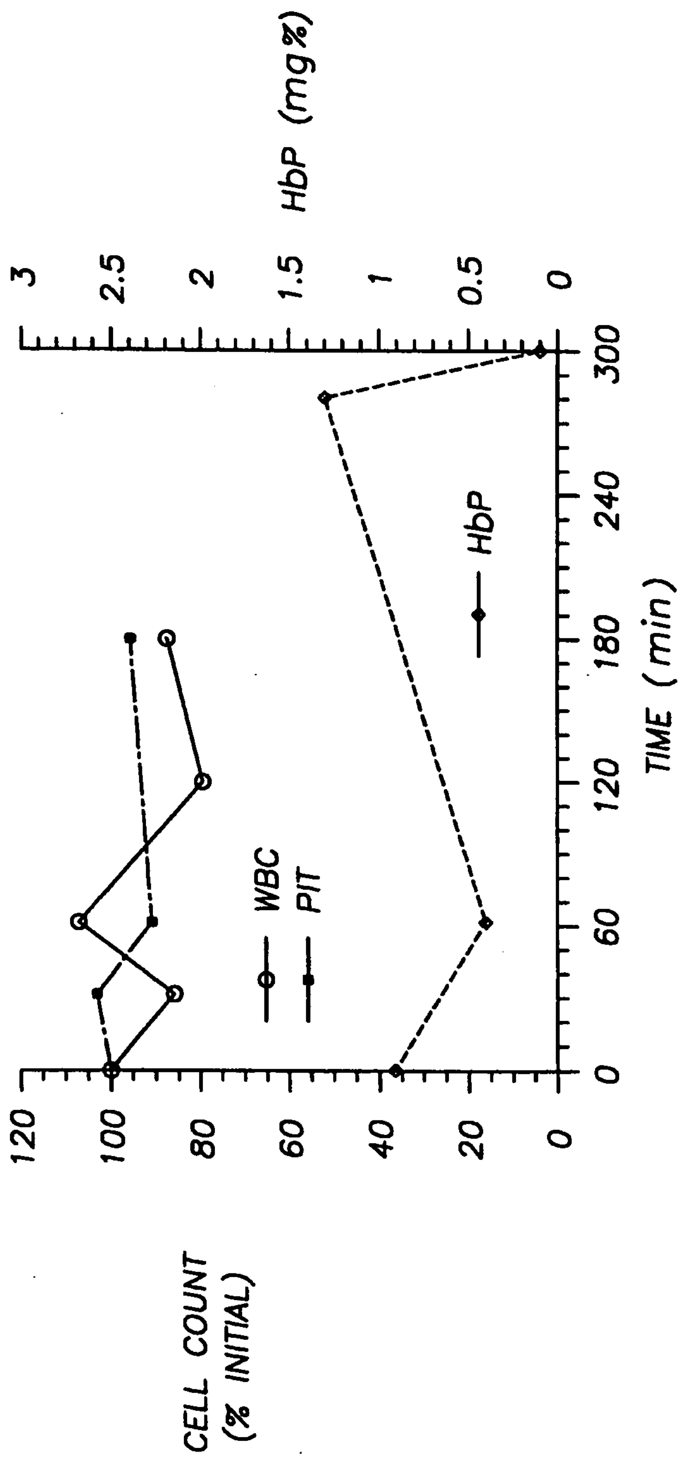

% CONVERSION
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
180
TIME (min)

FIG.10

FIG.11


CELL COUNT
(% INITIAL)
120
100
80
60
40
20
0
HbP (mg%)
3
2.5
2
1.5
1
0.5
0
0
60
120
180
240
300
TIME (min)
WBC
PIT
HbP

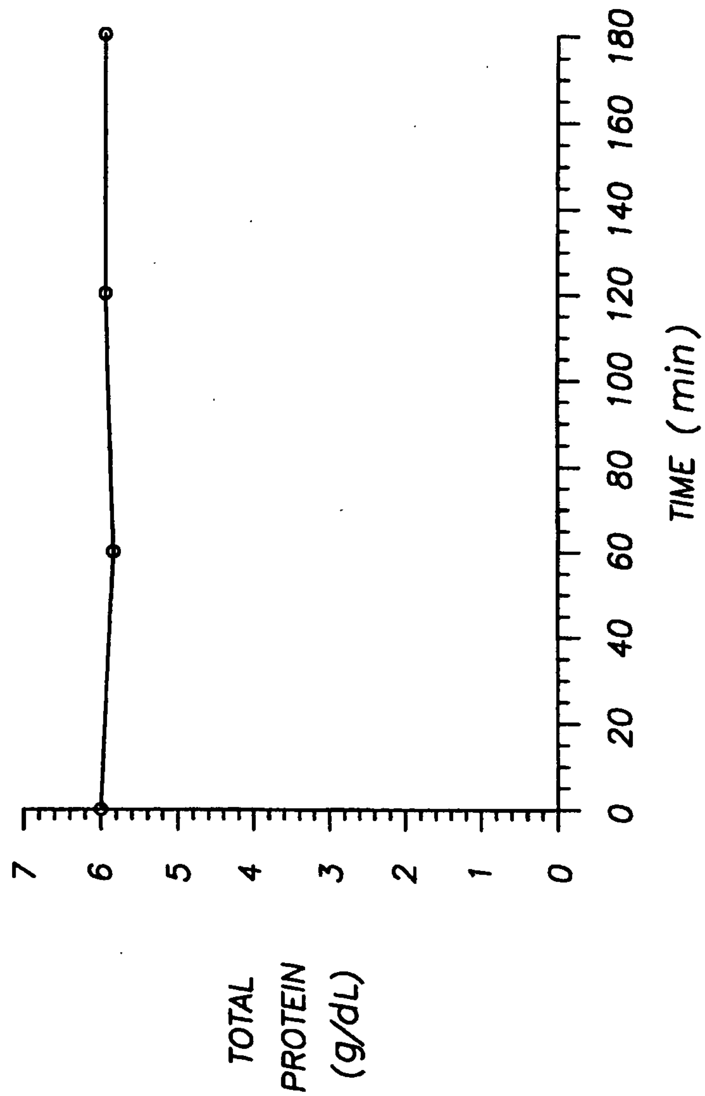

TOTAL
PROTEIN
(g/dL)
7
6
5
4
3
2
1
0
0
20
40
60
80
100
120
140
160
180
TIME (min)

FIG.12

FIG. 13

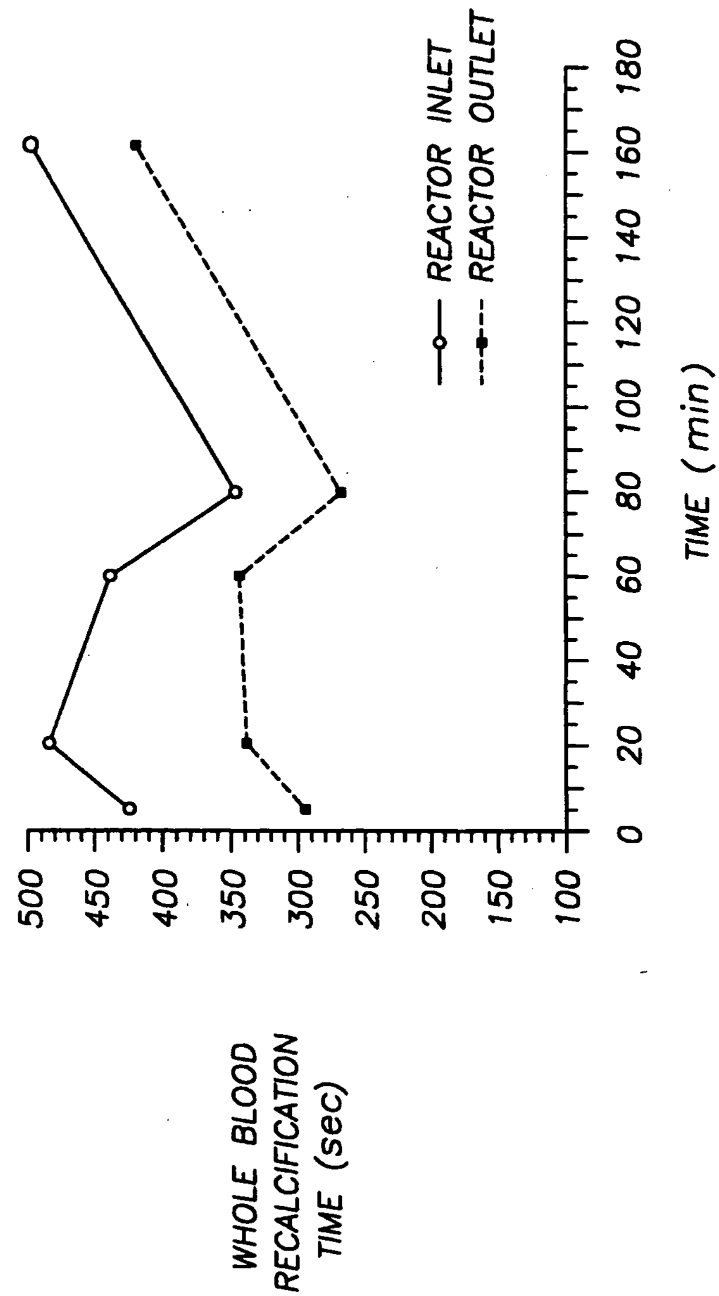
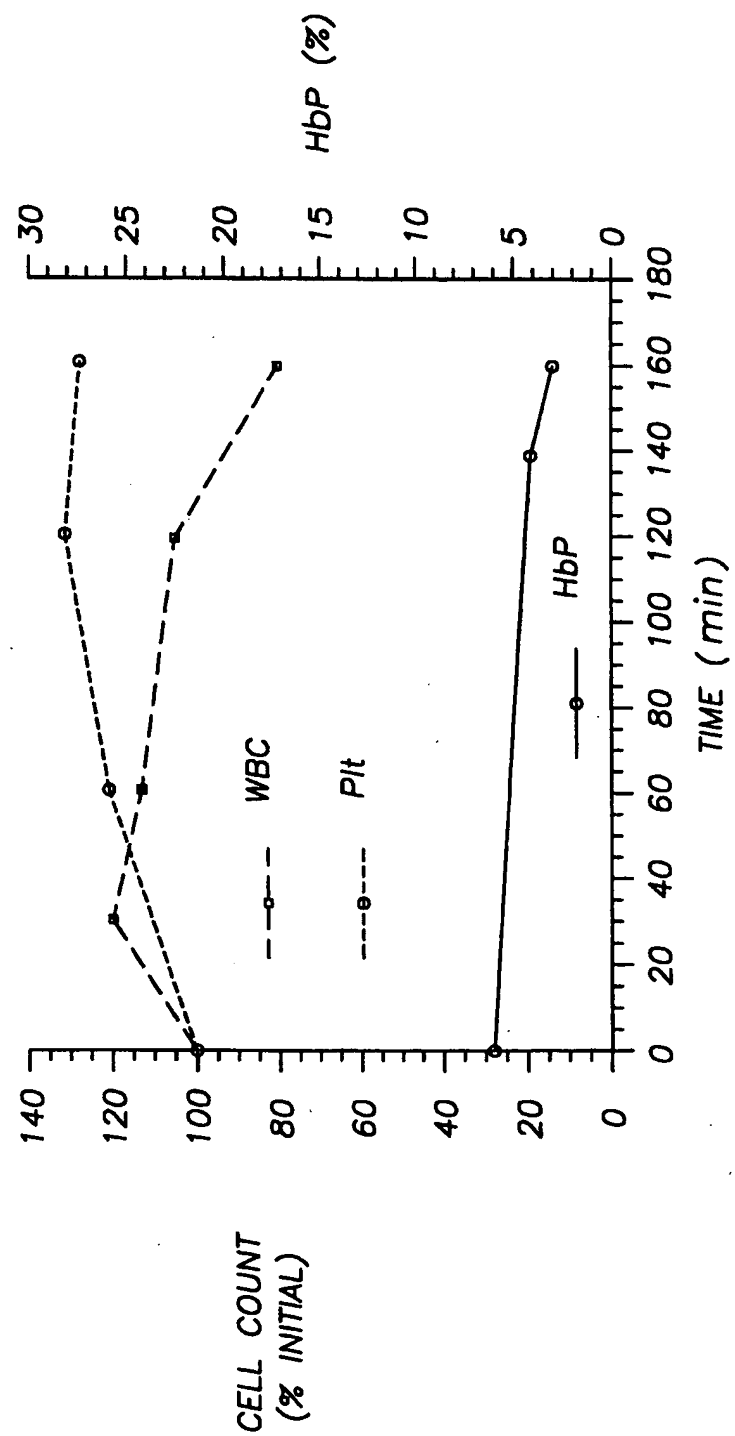

WHOLE BLOOD RECALCIFICATION TIME (sec)
500
450
400
350
300
250
200
150
100
0
20
40
60
80
100
120
140
160
180
TIME (min)
REACTOR INLET
REACTOR OUTLET

FIG. 14


HbP (%)
30
25
20
15
10
5
0
CELL COUNT
(% INITIAL)
140
120
100
80
60
40
20
0
WBC
Plt
HbP
0
20
40
60
80
100
120
140
160
180
TIME (min)

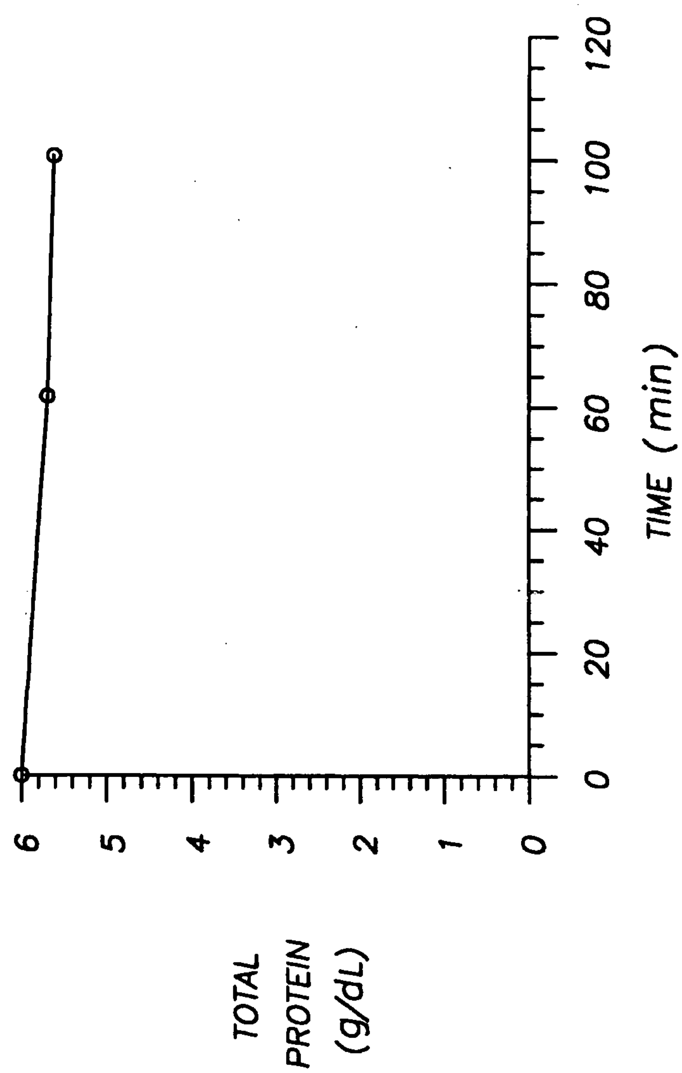


FIG.15

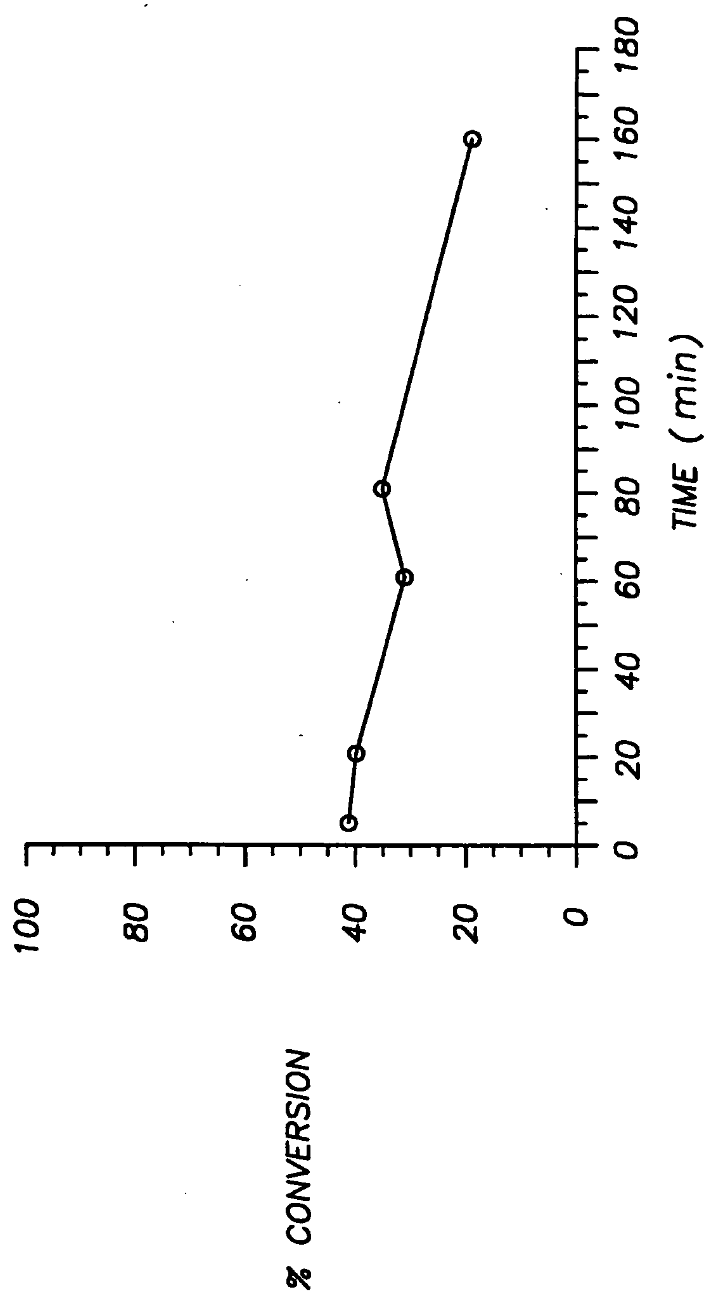
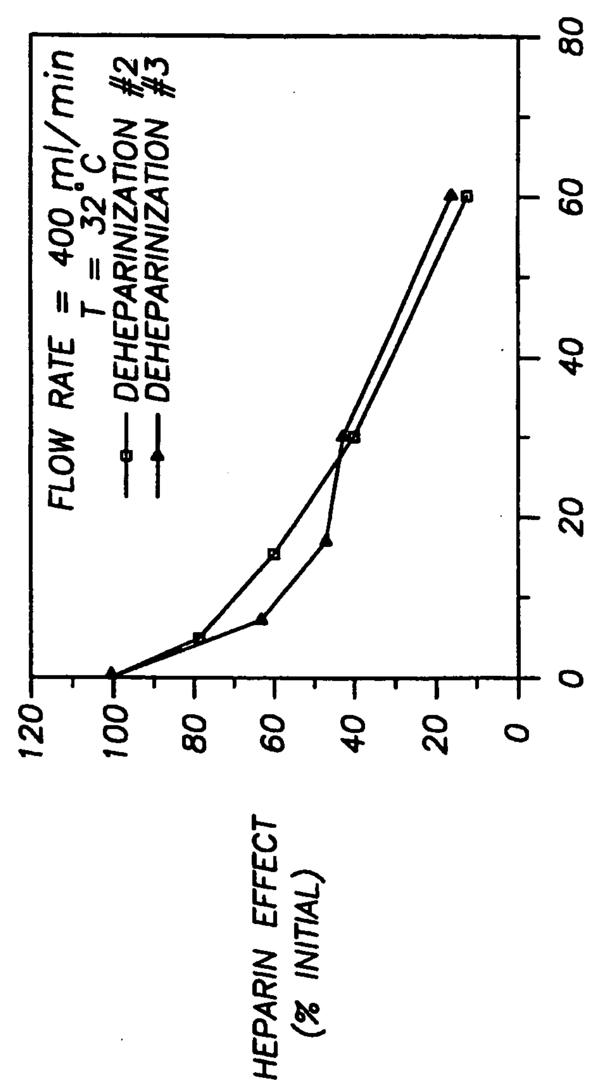

% CONVERSION
100
80
60
40
20
0
TIME (min)
0
20
40
60
80
100
120
140
160
180

FIG. 16

FIG. 17

PROFILE FOR HEPARIN REMOVAL IN MEMBRANE REACTOR
(ENZYME LOADING = 370 IU, 6-26-96)



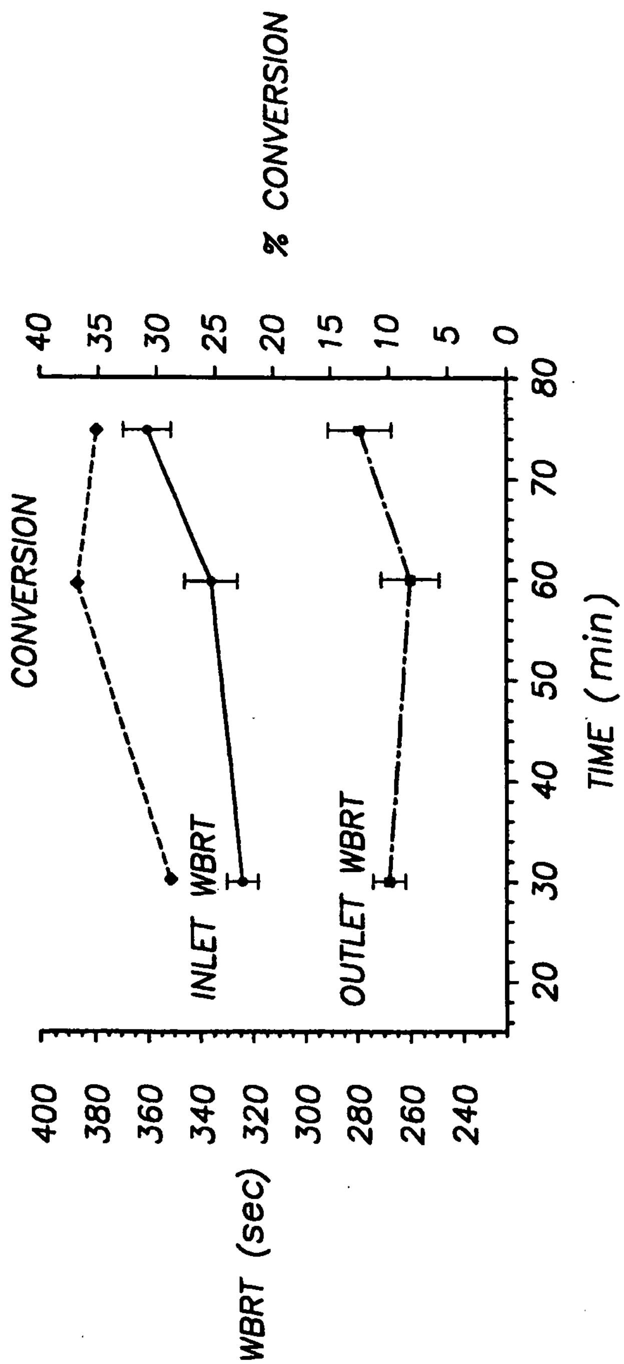

% CONVERSION
40
35
30
25
20
15
10
5
0
CONVERSION
INLET WBRT
OUTLET WBRT
20
30
40
50
60
70
80
TIME (min)
WBRT (sec)
400
380
360
340
320
300
280
260
240

FIG.18

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/24338

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01D63/16 A61M1/34 B01D65/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01D A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 00922 A (MEMBREX, INC.) 8 February 1990 see page 16, line 1-17 - page 10; claims 1,17-20	1-4
A	EP 0 310 205 A (W.F.MCLAUGHLIN) 5 April 1989 see claims; figures	1,23,24, 35
A	EP 0 231 623 A (HEMOLOGICS INC) 12 August 1987 see the whole document	1-35
A	WO 97 32653 A (RESEARCH MEDICAL, INC) 12 September 1997 see claims 1,32-35	1,6,7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 1999	06/04/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Cordero Alvarez, M

2

International Application No
PCT/US 98/24338

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 88 01193 A (HEMASCIENCE LABORATORIES, INC) 25 February 1988 see claims	1
A	EP 0 464 707 A (TERUMO KK) 8 January 1992 see claims	1
A	DE 34 06 562 A (FRAUNHOFER-GESELLSCHAFT ZUR FÖRDERUNG DER ANGEWANDTEN FORSCHUNG E.V.) 29 August 1985 see claims 1-10	1,7

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/24338

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
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			US	5000848	A	19-03-1991
EP 310205	A	05-04-1989	AT	50156	T	15-02-1990
			AT	108693	T	15-08-1994
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			CA	1261765	A	26-09-1989
			DE	3587885	D	25-08-1994
			DE	3587885	T	03-11-1994
			EP	0177564	A	16-04-1986
			JP	1845162	C	25-05-1994
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			JP	4023544	B	22-04-1992
			JP	61501494	T	24-07-1986
			US	5194145	A	16-03-1993
			WO	8504112	A	26-09-1985
			US	5738792	A	14-04-1998
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			US	4871462	A	03-10-1989
			US	4808307	A	28-02-1989
WO 9732653	A	12-09-1997	AU	2212897	A	22-09-1997
			CA	2247031	A	12-09-1997
			EP	0892664	A	27-01-1999
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			AU	7875387	A	08-03-1988
			CA	1289473	A	24-09-1991
			DE	3772749	A	10-10-1991
			EP	0277994	A	17-08-1988
			JP	1502400	T	24-08-1989
			US	4919817	A	24-04-1990
			US	5053121	A	01-10-1991
EP 464707	A	08-01-1992	JP	4058957	A	25-02-1992
			DE	69121326	D	19-09-1996
			US	5254248	A	19-10-1993
DE 3406562	A	29-08-1985	NONE			